A versatile synthesis of ellipticines.

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A VERSATILE SYNTHESIS

OF

ELLIPTICINES

A Thesis Submitted by

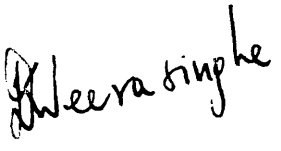
DEEPTHI KUMAR WEERASINGHE

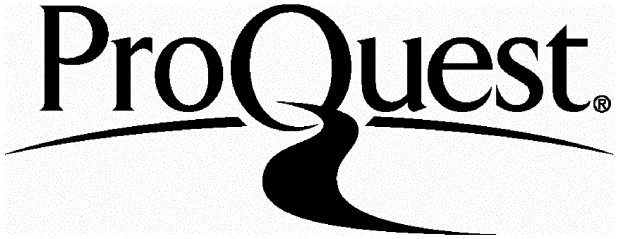
for the Degree of Doctor of Philosophy

of

The University of Bath

1981





for PUSHPA

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I am especially indebted and grateful to Dr. Malcolm Sainsbury for his guidance, invaluable suggestions and tolerance throughout this project.

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CONTENTS

SUMMARY

This thesis describes attempts to synthesise ellipticines for biological assessment in acceptable yields. It begins with a re-investigation of a procedure recommended for the preparation of 9-aminoellipticine and demonstrates that it is unacceptable when applied to large scale work.

Alternative constructions have been sought principally directed towards the formation of pyridylethylindoles which may be ring closed to ellipticines by the application of techniques commonly used in this laboratory. This study has culminated in a novel synthesis of 3-(3'-pyridyl)butanal and its indolisation with various arylhydrazines under the conditions of the Fischer reaction and in this way 7-methyl-, 7-fluoro-, 7-chloro- and 9-methoxyellipticines were synthesised.

INTRODUCTION

INTRODUCTION

CANCER AND ELLIPTICINE

Cancer may be defined as a neoplastic growth that has the ability to invade surrounding tissues and be disseminated by the blood stream and lymphatics. Numerous biochemical studies have been undertaken in attempts to define biochemical alterations associated with the development of carcinogenesis, biochemical characterisation or differentiation of cancerous from normal tissues and systematic changes (Fig. 1)[1] in the tumour host.

Characteristic dissemination of most cancers increase the difficulties of physical elimination by surgery and radiation. On the other hand chemotherapy and to some extent immunotherapy are not localised in their effects and thus have greater potential at least in theory. However, it is unlikely that any one procedure has universal application and in many present day circumstances a complementary approach is used to combat this disease.[2,3]

The synthesis of substances with anti-neoplastic activity is fashionable,[4] but despite the abundance of active compounds only a handful pass the protocols demanded prior to clinical adoption. These are:

(i) low mammalian toxicity, both acute and chronic;

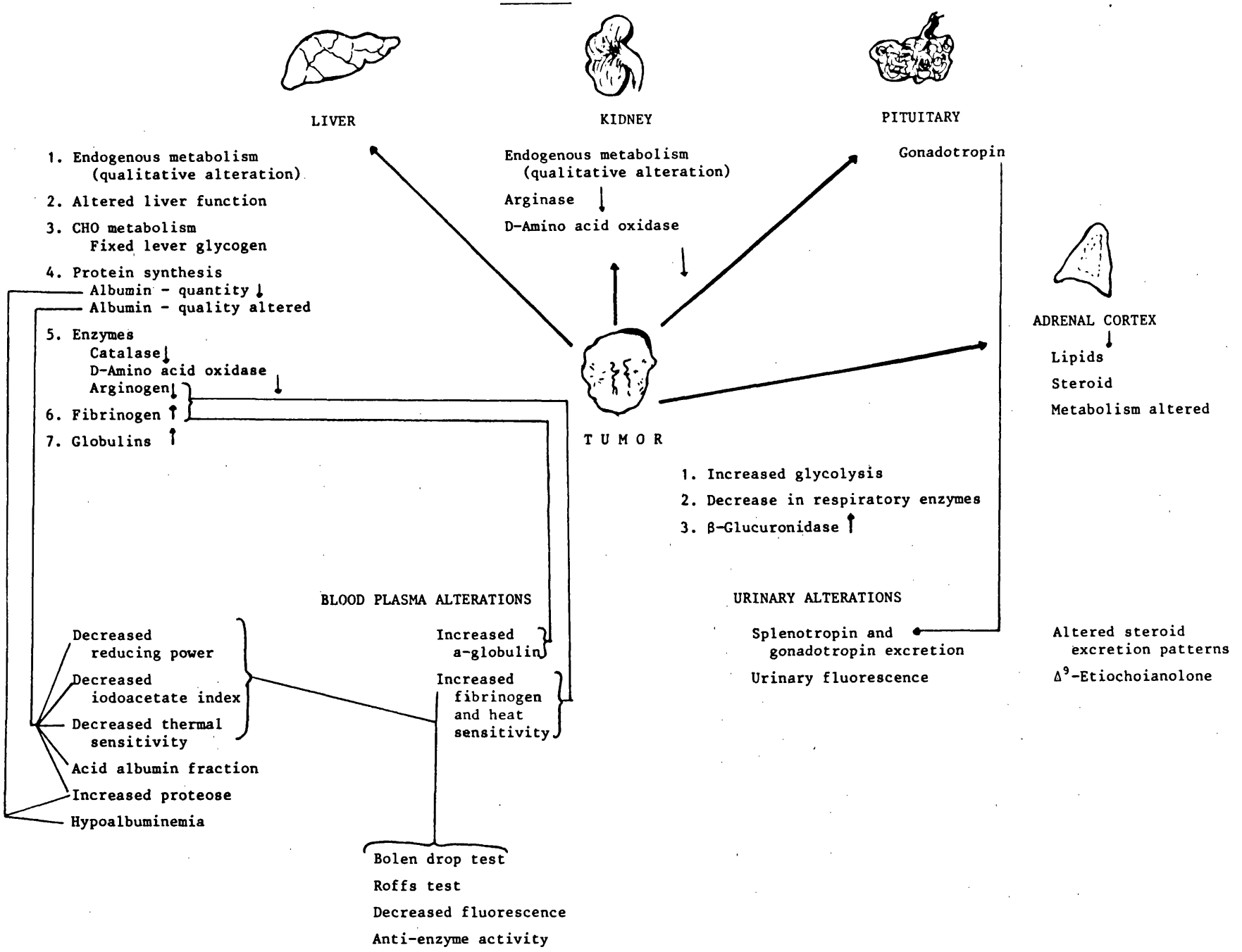
(ii) wide spectrum of high, specific and reproducible activity against tumours;

(iii) an acceptable mode of action and metabolism;

(iv) easy administration and stability on storage.

Most anti-neoplastic drugs in clinical use are supposed to be highly specific, acting upon cancerous rather than healthy

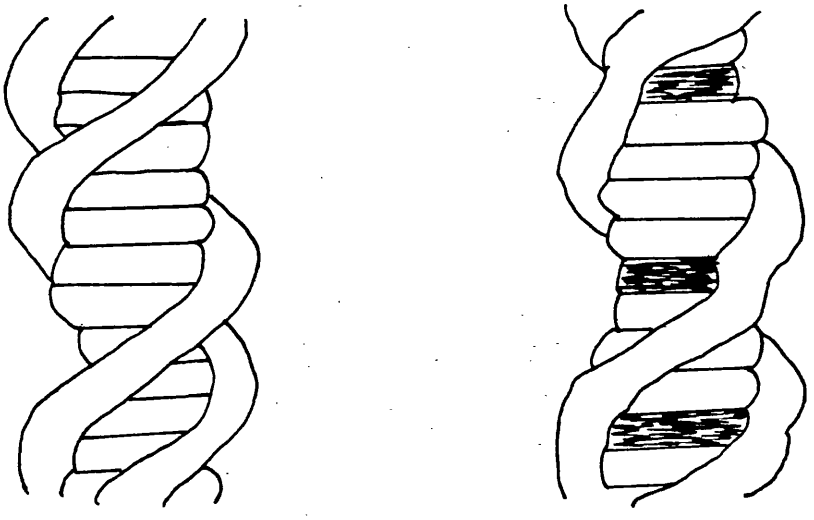
FIGURE 1


LIVER
KIDNEY
PITUITARY
1. Endogenous metabolism (qualitative alteration)
2. Altered liver function
3. CHO metabolism
Fixed lever glycogen
4. Protein synthesis
Albumin - quantity ↓
Albumin - quality altered
5. Enzymes
Catalase ↓
D-Amino acid oxidase
Arginogen ↓
6. Fibrinogen ↑
7. Globulins ↑
Endogenous metabolism (qualitative alteration)
Arginase ↓
D-Amino acid oxidase
Gonadotropin
ADRENAL CORTEX
Lipids
Steroid
Metabolism altered
TUMOR
1. Increased glycolysis
2. Decrease in respiratory enzymes
3. β-Glucuronidase ↑
BLOOD PLASMA ALTERATIONS
Decreased reducing power
Decreased iodoacetate index
Decreased thermal sensitivity
Acid albumin fraction
Increased proteose
Hypoalbuminemia
Increased a-globulin
Increased fibrinogen and heat sensitivity
Bolen drop test
Roffs test
Decreased fluorescence
Anti-enzyme activity
URINARY ALTERATIONS
Splenotropin and gonadotropin excretion
Urinary fluorescence
Altered steroid excretion patterns
Δ9-Etiochoianolone

cells, but Skipper et al[5] have shown that tumour cells are a million times more sensitive to bis-chloroethylnitrosourea than normal cells. Thus this apparent selective action depends partly on the paradox that many tumour cells proliferate less rapidly than normal tissues, and are thus less capable of repairing damage. Although it also could be that, in a situation when the cells defense system is preoccupied with the cancer, the impact of other foreign bodies are felt much more than under normal conditions.

The problem is poorly understood and this is one of the reasons why it is so difficult to design a really effective drug. Some knowledge of the mode of action, although not the selectivity, is available in the case of cytotoxic agents which act by intercalation with D.N.A.

The ability of drugs to intercalate, is related to their stereochemical parameters, size, planarity (or near planarity) and the electronic configuration. Intercalators fit into the cavities of the double-coiled helix and are secured by hydrogen bonding



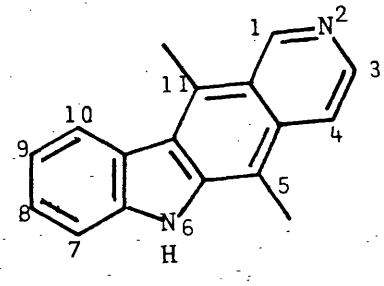
Normal DNA Distorted DNA

Schematic representation of distortion in DNA caused by intercalating substance.

and/or covalent bonding to the adjacent base pairs causing a localised torque of the dynamic structure which is manifested by an unwinding of the helix. Calculations (theoretical and experimental) of the magnitude of this interaction and the degree of the double helix unwinding for specific compounds has been used as a guideline for synthetic strategies, since the extent of unwinding often correlates with the degree of activity - at least against experimental tumours.

Interest in natural products as medicinal agents[6] is as old as mankind and it is not surprising that some should prove to be useful anti-cancer agents, often acting as intercalators. One such compound is ellipticine (1), originally isolated by Goodwin[7] from *Ochrosia elliptica* and subsequently found in other species of this genus and in plants of the *Aspidosperma*, *Tabernamontana* and *Hazunta* generae of the *Apocynaceae* family.[8] The genus *Ochrosia* consists of ~36 species of trees or woody shrubs mainly native to tropical Asia, Oceania, the Mascarena and the Seychelle islands (Table 1).[9]

The alkaloid ellipticine more correctly 5,11-dimethyl-6-H pyrido[4,3-b] carbazole (1) is an arc-shaped molecule which has stimulated a great deal of interest due to its anti-neoplastic activity notably against human myeloblastic leukaemia[10-13] (Table 2). (Out of twelve patients treated, three completely recovered).



(1)

Ellipticine is accompanied in nature by its 9-methoxy derivative, which is also an anti-neoplastic agent, and it is thought that they both interact with the D.N.A. during the

TABLE 1

PLANT	SYNONYM	ALKALOID	SOURCE
Ochrosia balansae, Guill.	Excavatia balansae, Guill	Ellipticine Aricine Isoreserpiline Reserpiline	New Caledonia
Ochrosia elliptica, Labill.	Ochrosia parviflora, G. Don Ochrosia noumeensis, Baill. Bleekaria elliptica, Labill. Excavatia elliptica, Labill. Cerbera parviflora, F. Forst. Ochrosia oppositofolia, K. Schum. Ochrosia moorei, F. Muel Bleekaria calocarpa, Hassk.	Ellipticine 9-Methoxyellipticine Elliptinine Elliptamine Isoreserpiline (Elleptine)	New Caledonia Florida (transplanted) Australia (transplanted) Mascarene Islands
Ochrosia sandwicensis, A. Gray	Bleekaria calocarpa, Hassk. Ochrosia tuberculata, Pichon	Ellipticine 9-Methoxyellipticine 10-Hunterburnine-a-Metho-chloride 10-Hydroxydihydrocory-nantheol methochloride N-Methylisoreserpilinium-chloride (Holeinine)	Hawaii
Aspidosperma ulei, Mgf.	Aspidosperma vergasii A.DC.	Guatambuine 3,4-Dihydroolivacine 3,4-Dihydroellipticine N-Methyltetrahydroellipticine Uleine	Brazil
Aspidosperma subincanum, Mart.	"Quillo-bordon"	N-Methyltetrahydroellipticine Ellipticine 3,4-Dihydroellipticine 3,4-Dihydroellipticine-methonitrate Ellipticine methonitrate Olivacine	Peru
Ochrosia glomerata, Valeton		Isoreserpiline Elliptamine Ellipticine Methoxyellipticine	New Guinea
Ochrosia maculata, Jacq.	Ochrosia borbonica, Gmel. Cerbera undulata "Bois jaune"	9-Methoxyellipticine Reserpine Ellipticine	Reunion Island Sri Lanka Mascarene Islands Java, Mauritius
Ochrosia vitiensis	Bleekeria vitiensis, Mgf. Excavatia vitiensis	Ellipticine 9-Methoxyellipticine Isoreserpiline-4-indoxyl Holeinine Bleekerine	Fiji
Aspidosperma vargasii, A.DC.		N-Methyltetrahydroellipticine 9-Methoxyolivacine Uleine Apparicine Desmethluleine Guatambrine	Venezula
Ochrosia coccinea, Miguel	Excavatia coccinea, Tejs & Bin. Lactaria coccinea	9-Methoxyellipticine Reserpine Isoreserpiline Elliptamine Ellipticine	New Guinea Java Australia

TABLE 2

ELLIPTICINE DERIVATIVE	pKa	Kap (pH 7.4)	ϕ	Log K_E^+	Sarcoma 180 C/T index	Ehrlich carcinoma C/T index	ACTIVITY
6-isopentyl	4.7	10^4	6.3	8.8	-	-	0
6-isopentyl-9-methoxy	4.5	10^4	6.7	-	-	-	-
5,11-desmethyl	6.35	1.0×10^4	5.08	-	-	-	0
11-desmethyl	6.3	2.4×10^4	5.52	-	-	-	0
9-methoxy	6.8	1.0×10^5	5.7	6.8	5.99	5.98	90
ellipticine	9.1	1.5×10^5	5.2	9.0	8.65	18.78	94
9-bromo	6.1	4.0×10^5	6.92	0.0	-	-	0
6-methyl	6.1	4.0×10^5	6.92	10.2	-	-	92
9-amino	9.8	1.2×10^6	6.08	4.0	-	-	2
6-methyl-9-methoxy	6.45	2.0×10^6	7.3	5.0	-	-	50
9-hydroxy	9.8	2.0×10^6	6.15	12.0	4.06	1.77	99.96
9-methoxy-6-acetyl	-	-	-	-	2.8	2.42	-
1,2,3,4-tetrahydro-9-methoxy (HCl)	-	-	-	-	5.14	3.84	-
8,9-dimethoxy	-	-	-	-	inactive	inactive	-

ϕ = Unwinding angle; Activity = % of L 1210 cells killed by 1/3rd of LD_{50}. 9-bromoellipticine does not intercalate.

A compound was considered to show significant anti-tumour activity if the ratio of the average tumour weight of the treated (T) animals was 50% or less of the average tumour weight of the untreated control (C) animals (C/T index > 2).

metaphase or the anaphase of mitosis.

Although there is some confusion over the details of this process there seems to be no doubt that these alkaloids do actually bind to the base pairs of the super coiled helix, and complexes between D.N.A. and ellipticine have been isolated.[14,15]

In fact 9-methoxyellipticine is more active than ellipticine and has a greater effect on the L 1210 murine leukaemia than many established anti-cancer drugs, having significant test ratings against ten out of seventeen experimental mammalian tumour systems.[10,16,17]

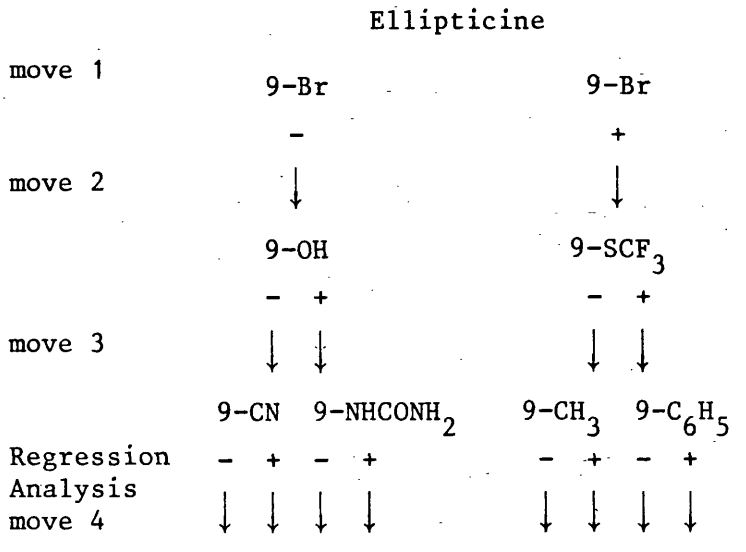
Some derivatives have been made and tested and it has been suggested that skeletal modifications of ellipticine at positions other than C-9 or N-2[18,19] tend to diminish its anti-cancer effect.[20] At the time this work was published the compounds included in Table 2 still reflect the ease of synthesis rather than an attempt to establish the structural requirements for optimal therapeutic action.

Within the last two decades one approach to rationalising synthetic objectives is the so-called Hantsch analysis[21] (after Corwin Hantsch the leading exponent). Such an approach is most meaningful when the substrate is a rigid molecule, as is the case with ellipticine. It consists of selecting two or three lead substituents which have very different electronic and physical characteristics and observing the effect that they have upon the biological properties of the parent molecule. Following positive or negative results other substituents are employed which span the properties of the first set. Gradually by following positive leads, the best choice of derivatives becomes apparent.

Hantsch himself has suggested suitable lead molecules to unravel the ellipticine problem, all based arbitrarily upon the 9-position. Interestingly one of these targets, 9-hydroxy-ellipticine, has proven to be at least one hundred times as active as the parent molecule.[22] This dramatic discovery has tended to close the minds of other workers to the possibilities for substitution at other positions and even to completing the remaining elementary steps of the Hantsch analysis.

Topliss[23] developed a similar, pragmatic approach which was subsequently referred to as the "Topliss Tree". A scheme for ellipticine and based upon Hammett effects (electronic) and partition properties, octanol vs water (physical) is shown in the accompanying diagram, where the symbols + and - indicate more or less active. Thus should 9-bromoellipticine be more active than ellipticine the next derivative to be made is the

"Topliss Tree"



9-trifluromethylmercapto. If less active then the target is 9-hydroxyellipticine. Each functional group in such a tree is chosen to span the combination of electronic and physical properties and the choice can be made more sophisticated by

utilizing more than two properties. However, the simple tree is most valuable in giving a range for an initial study. After the results have been obtained one should resort to regression analysis for guidance in choosing future synthetic targets. Intervention of severe steric or metabolic factors can completely mask the interpretation of the analysis and limit the use of this approach. Furthermore, the system is only successful if the rate of pharmacologic testing is faster than the speed at which synthesis of derivatives can be accomplished.

In six retrospective cases cited by Hantsch,[23,24] the use of the Topliss decision rules to guide lead-optimising synthetic programmes would have identified the most active compound with considerably less chemical effort than that actually expended.

As part of a joint collaboration between French and British chemists an evaluation of the Topliss tree was commenced in 1973. The French workers were to examine the left-hand half and the Bath group the right. The work was a compromise since some compounds were easier to make than others. In preliminary studies 9-bromoellipticine and 9-aminoellipticine proved to be mutagenic, although the latter is more active than ellipticine itself. 9-Phenylellipticine is inactive and non-mutagenic, presumably because the bulky phenyl group prevents intercalation into D.N.A.

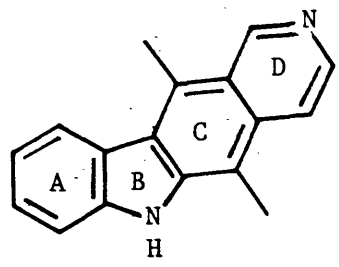
The loose collaboration broke down when the high activity of 9-hydroxyellipticine was discovered and much of the French effort was then directed to the preparation of salts of this compound for human clinical trials. It should be pointed out that modification of 9-aminoellipticine to the carbamate derivative was the next logical step. This move was not carried out. Similarly the selection of the 9-position was an arbitrary one and before one

can be certain that the problem is solved it is vital to follow a logical course of action and make available a wide variety of derivatives not only based on the 9-position but elsewhere in the tetracyclic system.

Such an aim is the motivation for much of the work described in this thesis which begins with a survey of synthetic routes[26] to the parent system.

SYNTHESIS OF ELLIPTICINE

The synthetic strategies to ellipticine involve three main types of ring fusion. Some representative examples of all three approaches are ennumerated in the sequel.



(2)

Type 1. Rings A + B forming an indole nucleus is condensed with an acetyl pyridine. This is followed by the formation and aromatisation of ring C.

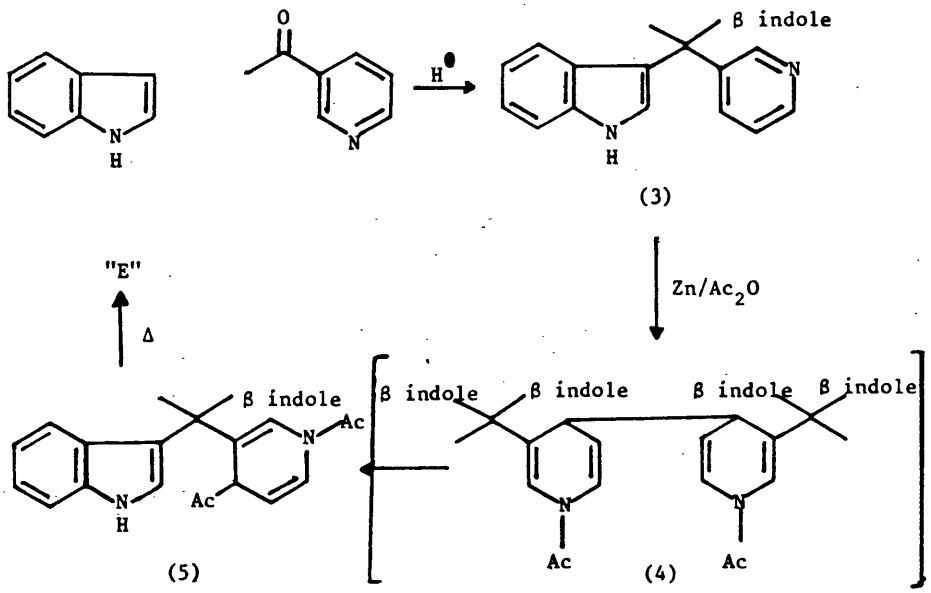
Type 2. Rings A + B + C as a carbazole unit are presynthesised and then the last ring D is built on from a formyl derivative using varying techniques such as the Pomeranz-Fritsch or Bischler-Napieralski ring closures.

Type 3. Rings C + D as tetrahydroisoquinolone and ring A as an arylhydrazine are coupled together to give a hydrazone. Ring B is then formed in a Fischer indolisation step followed by aromatisation of rings C + D.

Synthesis following type 1 procedures

Following the isolation of the alkaloid[7], Woodward's group[27] established the original structural assignment via a remarkably simple synthesis (route 1), but unfortunately the extremely low overall yield precludes its synthetic use.

The steps in the synthesis are as follows. First the condensation of two molecular equivalents of indole with one molecular equivalent of 3-acetylpyridine in acetic acid gave bis(3-indolyl)-1(3-pyridyl)ethane (3). Attempts to change the conditions so that a 1:1 reaction between indole and the pyridine took place failed, since the rate of the second reaction



ROUTE 1

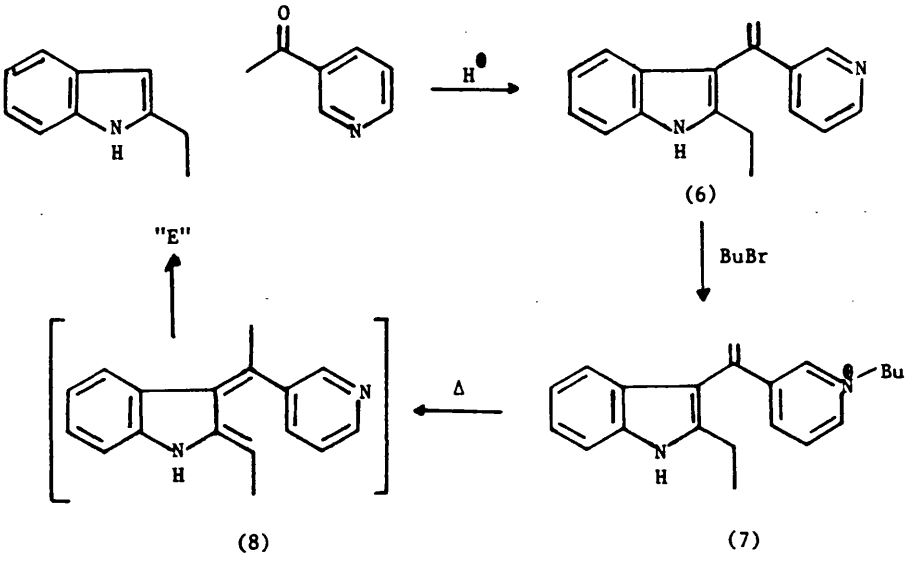
is faster than the initial one.

Characteristically Woodward attempted to restrain this undesirable reaction by modifying the conditions but without success and thus continued with what must be regarded as a second choice substrate for the remainder of the sequence. The "2:1 adduct" was subjected to a reductive acetylation using zinc and aceticanhydride.

This Wibaut-Arens[28] reductive acetylation is known to be sensitive to steric factors and is thought to proceed via the dimer (4), which then disproportionates into starting material and dihydropyridine (5). Although no yield is quoted for this stage it is likely that it was very low. Since the many non-bonded interactions present in the dimer (4) tend to make it a high energy species.

The final oxidative ring closure was also difficult, requiring the use of severe pyrolytic conditions and perhaps not surprisingly the yield of ellipticine overall was only 0.2%.

Much later, Bergman et al[29] modified this sequence. Here, (route 2) the propensity of simple indoles to react with two moles of ketone was inhibited by the use of a 2-substituted indole derivative. A Madelung reaction on propyl-o-toluidine gave 2-ethylindole which was condensed with 3-acetylpyridine in refluxing ethanolic hydrochloric acid to give the "1:1 adduct" (6).



ROUTE 2

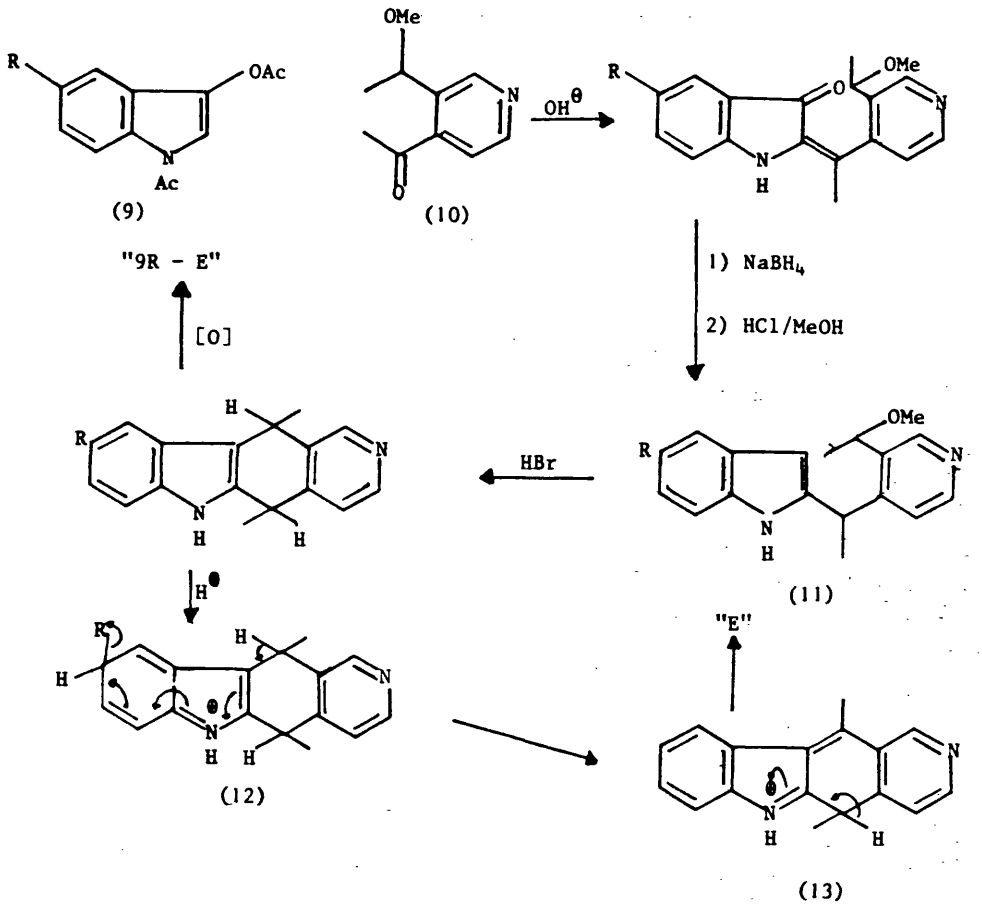
The indolyl pyridyl ethene (6) was quaternised by refluxing with n-butylbromide and the salt then pyrolysed to give ellipticine. It is thought that the salt isomerises to the triene (8) via [1,5]-suprafacial hydrogen shift, and the triene then undergoes an electrocyclisation reaction followed by the loss of butane.

In the event why it should be necessary to N-alkylate the pyridine nitrogen atom is not certain but if this is not done then the yield is very low. Possibly this mechanistic view is incorrect and the reaction proceeds via a stepwise nucleophilic attack through the enamine unit of the intermediate (8).

The appeal of the synthesis is somewhat limited because

of the harsh pyrolysis step. This is specially important since many ellipticine derivatives appear to be thermally unstable.

In the early part of the last decade, the research group at Bath, developed a simple synthesis[30] (route 3) based on the indole (11). Base condensation of the diacetylindole (9) with 4-acetylpyridine (10) furnished E and Z isomers of the indolin-3-one which on subsequent reduction followed by acid dehydration gave the necessary indole (11) in high yield. Spontaneous ring closure and oxidation to ellipticine was achieved by refluxing the indole in 40% aqueous hydrogen bromide.

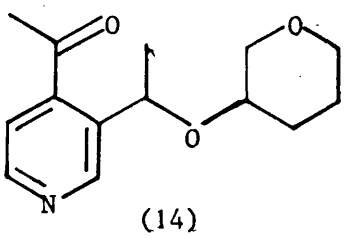


ROUTE 3

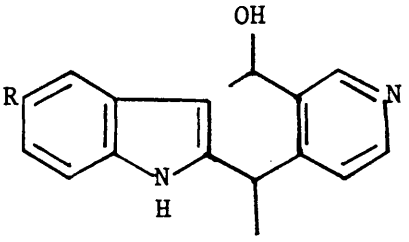
Unfortunately labile groups (NH_2, Br) tend to be eliminated in the oxidative process to yield a mixture of the desired product and the parent molecule.[25] The reason for this unfortunate side reaction is probably that strong protonating

conditions allows aromatisation of the dihydroellipticine as shown (12-13).

The probability of this explanation is enhanced by the fact that only those groups capable of leaving as anions are lost. Other substituents e.g. phenyl are retained. It is necessary therefore to arrive at the fully aromatic tetracyclic species rather than the dihydro form and so by using the pyridine (14) and oxidation of the deprotected product (15) in dimethylsulphoxide and acetic anhydride it was possible to obtain 9-aminoellipticine in good yield.

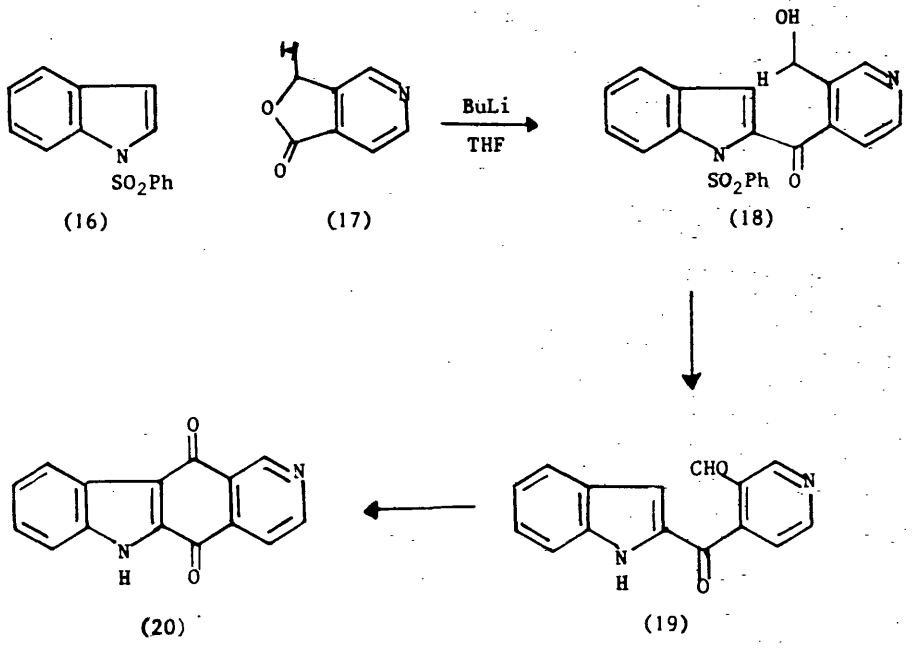


(14)



(15)

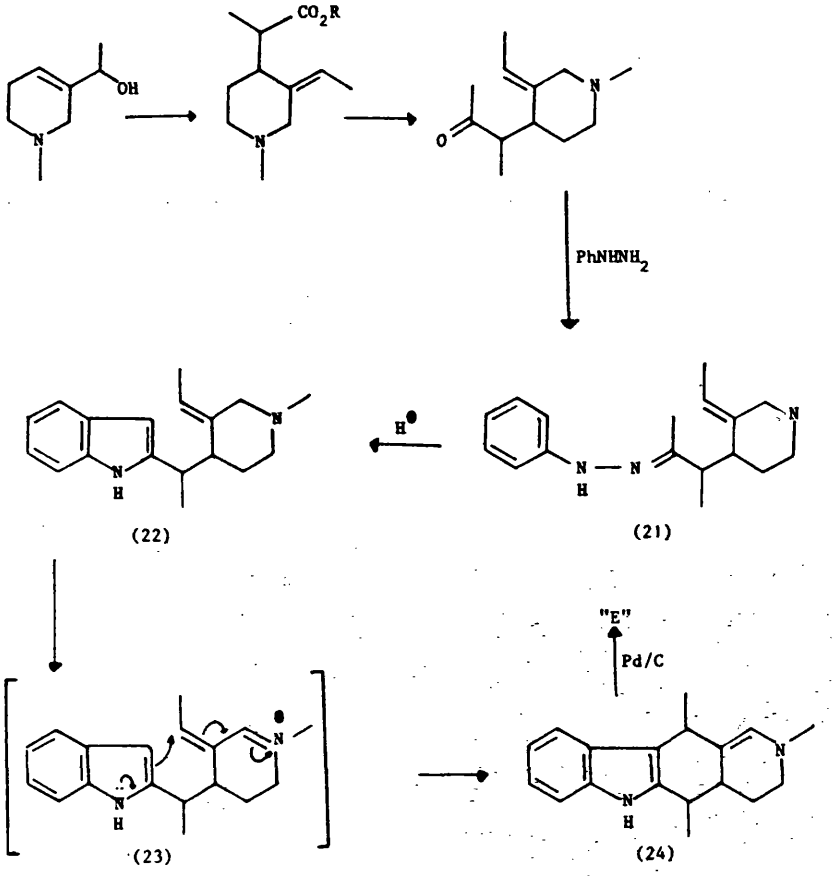
Recently Joule et al[31] (route 4) condensed the pyridinyl lactone (17) with the 2-lithiated indole (16) to give the



ROUTE 4

alcohol (18). This on oxidation gave the aldehyde (19) which was then oxidatively ring closed to give the quinone (20). This product was treated with organolithium reagents to give 5,11 substituted ellipticine derivatives. A similar synthesis has been announced by the Canadian group lead by Snieckus.[32]

A final example of the type 1 synthetic approach is provided by French chemists lead by Potier[33] (route 5).

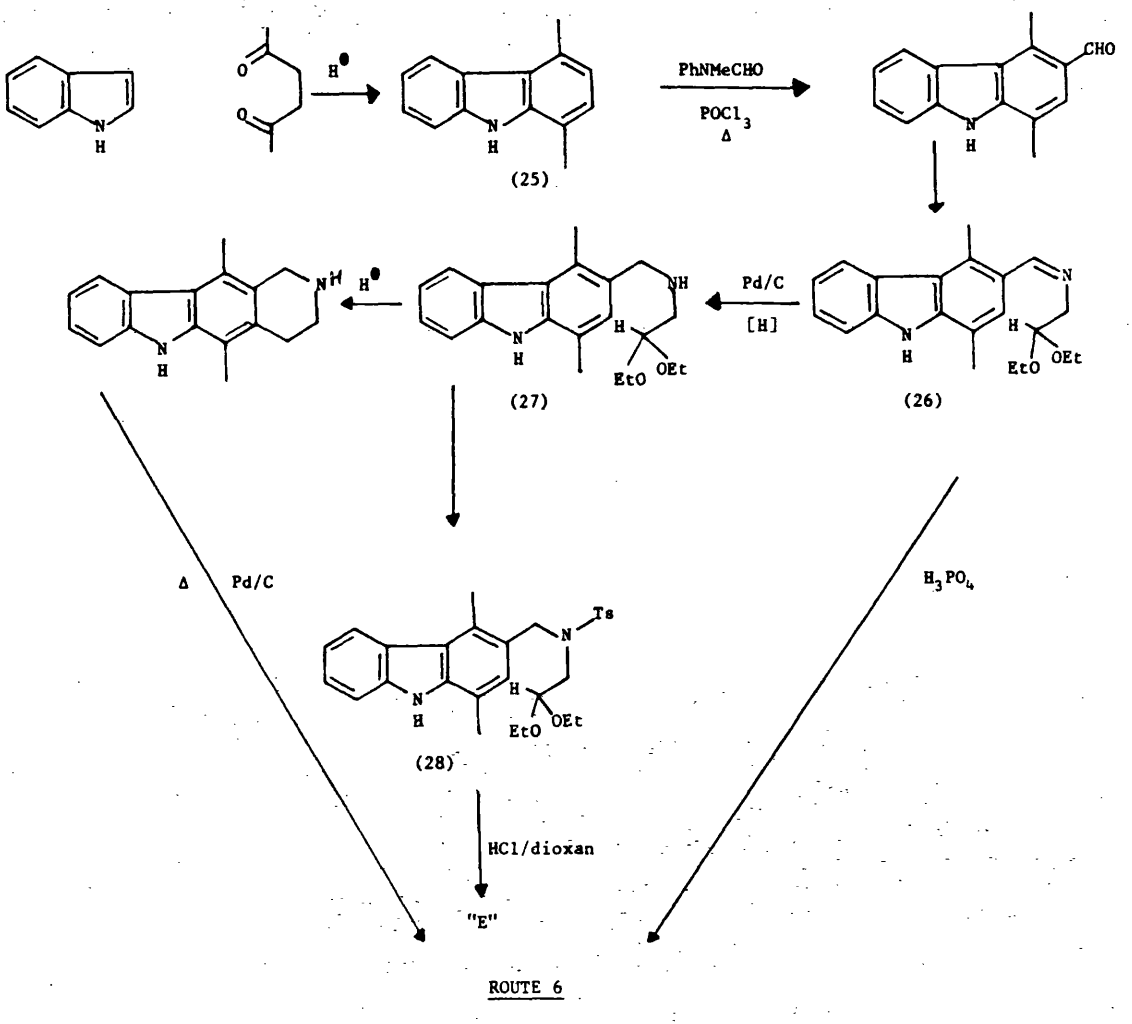


ROUTE 5

Their approach required the hydrazone (21) which was cyclised to the indole (22). On treatment with hydrogen peroxide this gave the piperidone-N-oxide which with trifluoroacetic anhydride afforded the imonium ion (23) which cyclised spontaneously to the enamine (24) in high yield. Finally this tetrahydro product was dehydrogenated to ellipticine by heating with palladium on charcoal.

Synthesis following type 2 procedures

There have been several synthetic strategies from carbazoles to pyrido[4,3-b]carbazoles,[34] but by far the most versatile of them is an approach pioneered by Cranwell and Saxton[35] (route 6). This route is still in use today and begins

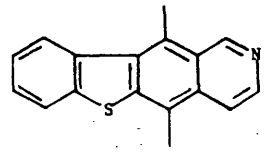


ROUTE 6

with a condensation between indole and hexan-2,5-dione to give 1,4-dimethylcarbazole (25). The 3-formyl derivative is then prepared by a Vilsmeier reaction and condensed with 2,2-diethoxyethylamine to give the Schiff's base (26). Cranwell and Saxton were unable to cyclise this compound directly and had to reduce it to the amine prior to ring closure. Later this problem was surmounted by Dalton et al[36] who used concentrated

phosphoric acid as the reagent, effecting a Pomeranz-Fritsch type cyclisation on the Schiff's base (26) itself giving ellipticine in high yield.

Although this direct cyclisation improved the overall yield to the parent alkaloid it was found that electron donating substituents in the non-methylated benezenoid ring promoted formylation into other sites in addition to the desired 3-position and that electron-withdrawing substituents in the ring severely limited the cyclisation reaction. The harsh final Pomeranz-Fritsch conditions preclude the use of this route for the synthesis of derivatives containing labile groups, but despite these limitations this synthesis was applied to a number of derivatives including the two related oxa and thioxa tetracycles (29) and (30).[37]



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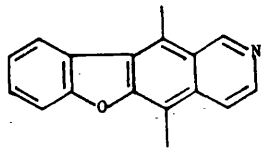

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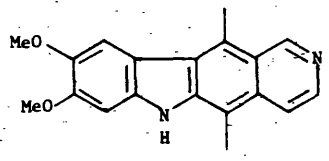

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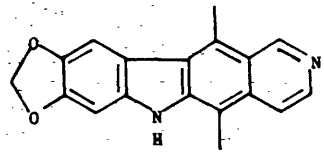


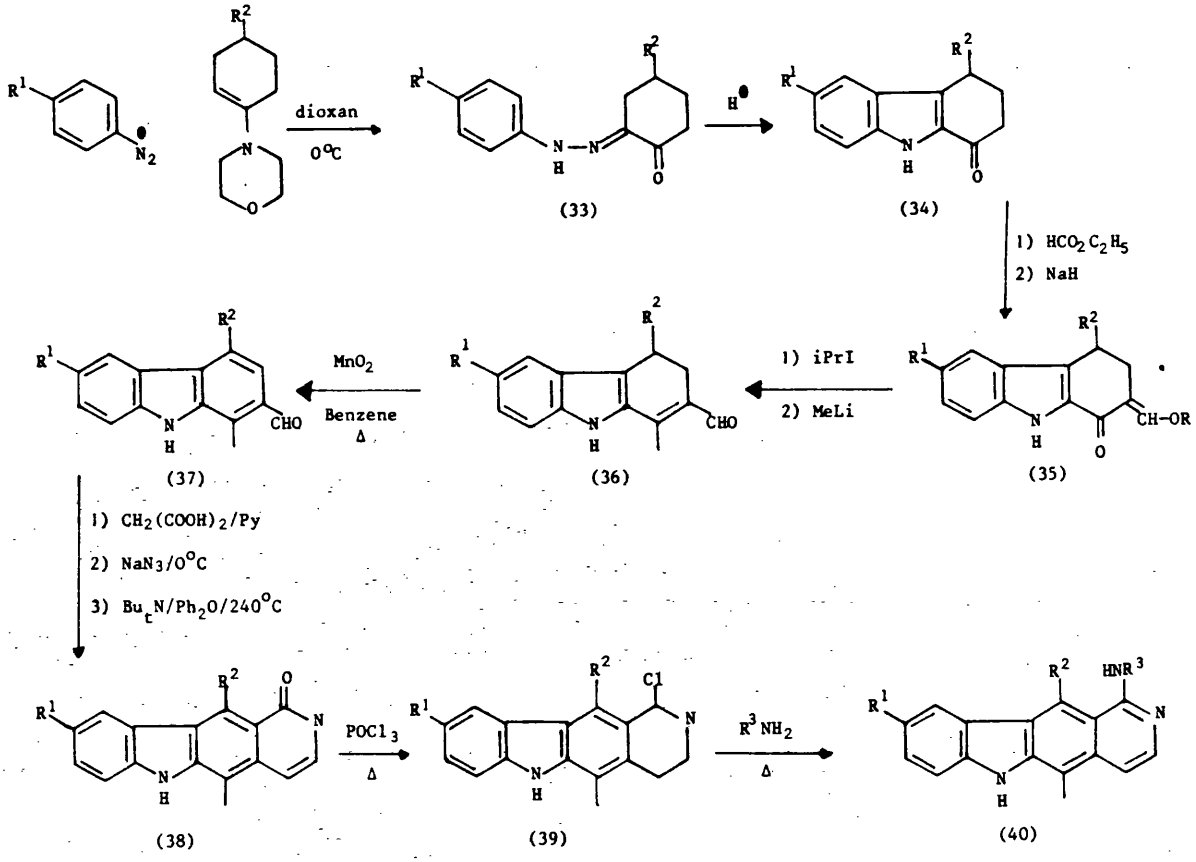
(32)

In 1975, a further improvement to this route was worked out on both sides of the Atlantic.[38] Here, the reduced Schiff's base (27) was N-tosylated and cyclised with 6N hydrochloric acid at room temperature.

The major advantage of this route is that ring closure is accompanied by aromatisation of ring D through the loss of 4-methylphenylsulphinic acid, thus avoiding thermolysis over palladium on carbon. By this means the hitherto unobtained

derivatives (31) and (32) were prepared.

Very recently, Bisagni et al[39] have synthesised a series of new analogues following route 7. The Fischer indolisation of the hydrazone (33) and acylation of the resulting dihydrocarbazole (34) with ethylformate and sodium hydride gave the 2-hydroxymethylenedihydrocarbazole (35). Reaction with isopropyl iodide-yielded the ester which on the addition of excess methyl lithium and subsequent hydrolysis afforded the 2-formyldihydrocarbazole (36).



ROUTE 7

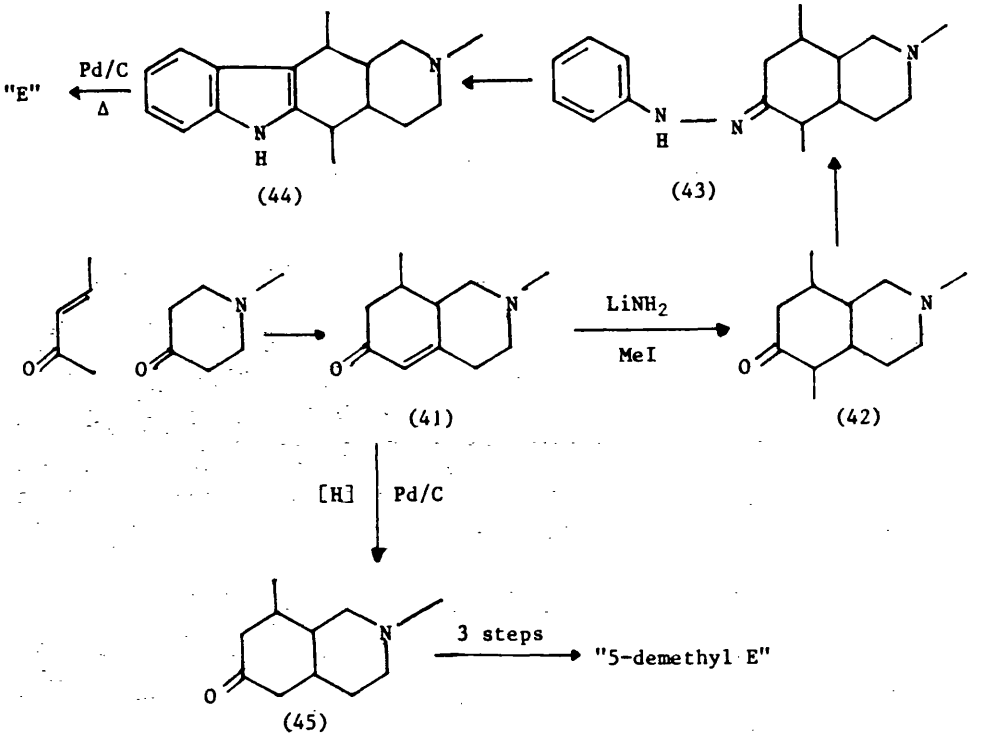
Ring C of the compound was aromatised by heating with manganese dioxide in boiling benzene and this gave the aldehyde (37) in high yield without apparently effecting disproportionation as might have been the case with palladium on charcoal or further oxidation onto the corresponding acid. In any event the process

can be performed on a large scale.

The elaboration of the D-ring was accomplished in three steps. First a Knoevenagel condensation of malonic acid with the aldehyde afforded a trans-acrylic acid which was transformed to the corresponding azide. Finally the pyrolysis of the azide effected cyclisation to the pyridone (38) which is converted into the chloro derivative (39) by heating with phosphorus oxychloride. The chloro compound behaves as an electrophile and reacts with primary alkyl amines to yield 1-alkyl amino ellipticines (40).

Synthesis following type 3 procedures

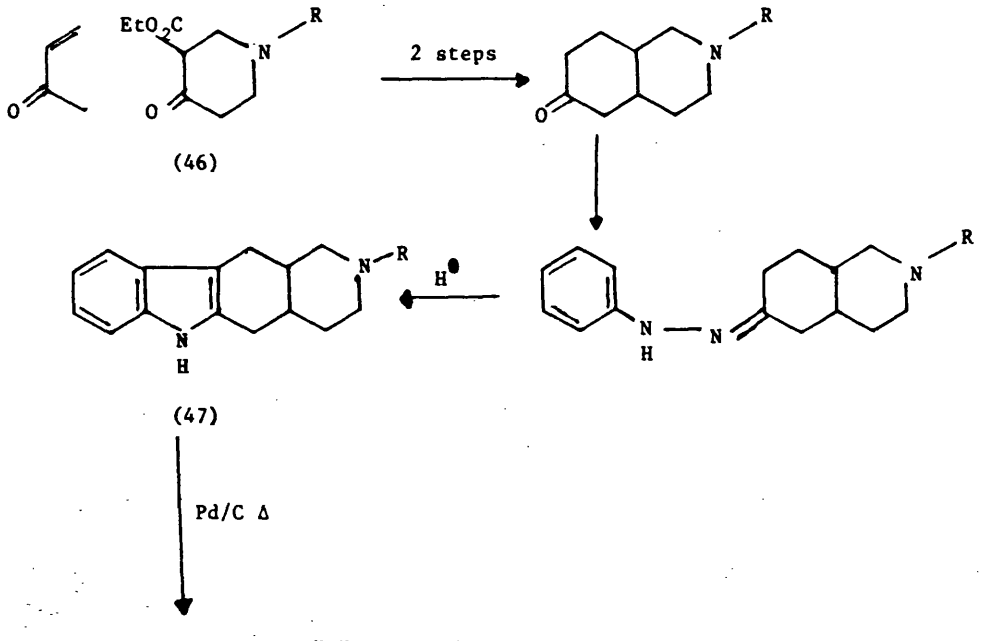
Following Woodward's initial effort, Stillwell[40] attempted an approach via an isoquinolone system (route 8). Here the



ROUTE 8

necessary decahydroisoquinolone (42) was prepared by a reductive Stork alkylation of the enone (41). Although model reactions worked well, certain steps in the actual synthesis were disappointing.

Recently Bergman and his co-workers[41] have reported Stillwell's experiments with minor modifications in the anticipation of better results. The isoquinolone (45) was formed by hydrogenation of the easily prepared decahydro analogue (41) and converted into 5,demethylellipticine in good yield. However the problem of inserting the 11-methyl group remains and this also applies to Rastogi's[42] work (route 9) in which 5,11-demethylellipticines were formed from methylvinyl-

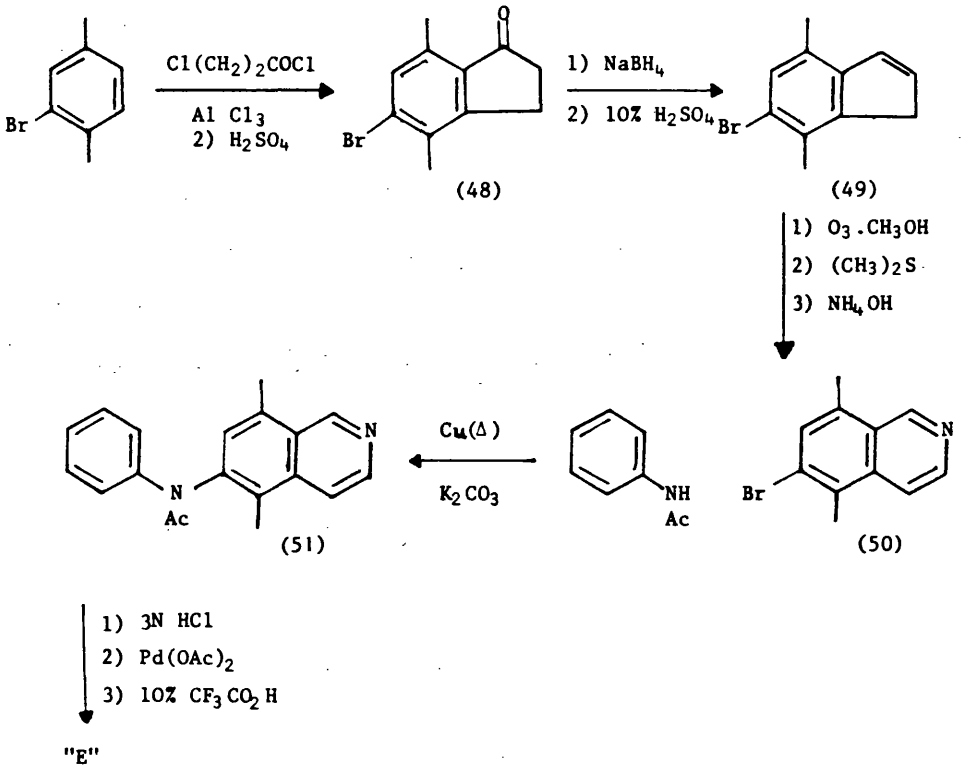


5, 11 - demethyl "E" and derivatives.

ROUTE 9

ketone and the piperidone (46) as initial starting materials. Hydrazone formation, followed by indolisation gave the tetracyclic systems (47) which were then aromatised over palladium on carbon.

Recently Miller and Moock[43] (route 10) using the same isoquinoline strategy coupled acetanilide with the bromo-isoquinoline (50) under Ullmann conditions to yield the N-acetylamine (51). After N-deprotection the parent amine was cyclised with palladium acetate in the presence of trifluoro-acetic acid.



ROUTE 10

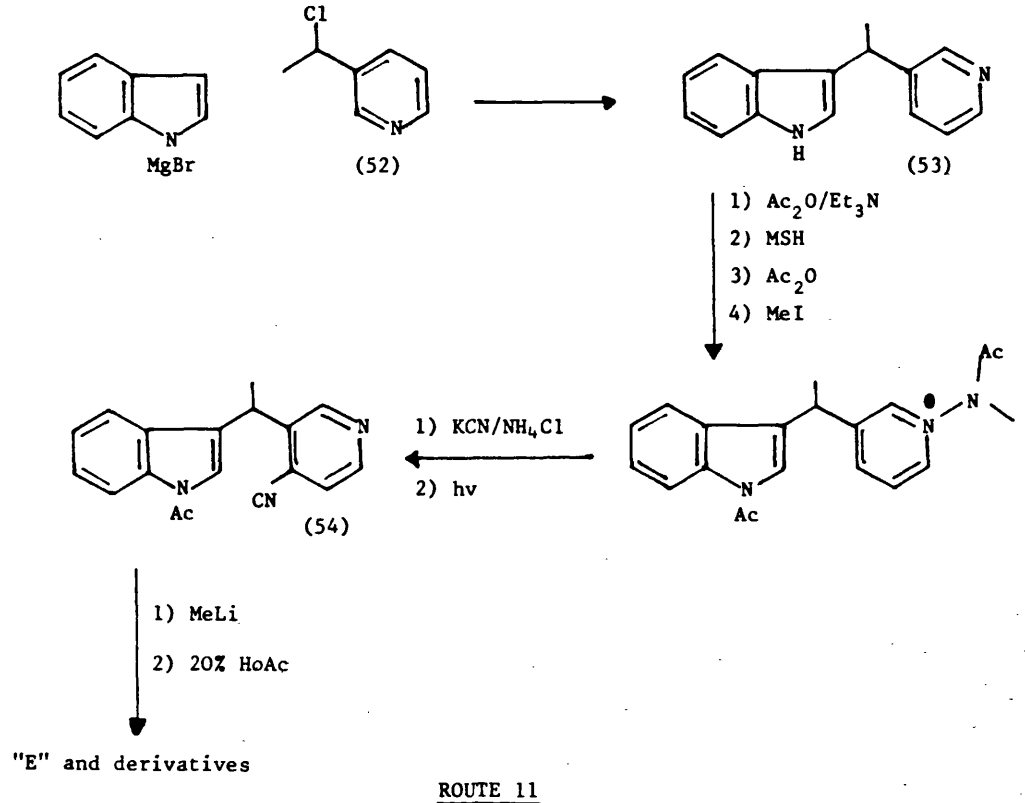
In order to prepare the necessary isoquinoline these workers effected a ring expansion of the indene (49) by ozonolysis to give an intermediate homophthalaldehyde which is directly reacted with ammonium hydroxide in a "one pot" procedure to give the fully aromatic isoquinoline.

Conclusions

A critical examination of the preceding studies makes it clear that some approaches are "once only" in the sense that they are far too complicated to allow general development or the conditions of ring closure or aromatisation, where applicable, are too harsh to enable some sensitive functions to survive without protection. The modified Cranwell, Saxton route obviously has the greatest potential for derivatives substituted in ring A providing they do not cause problems in the formylation step. But still one has to prepare the necessary carbazoles and access to structures substituted at positions other than 8-C is difficult.

For pyrido[4,3-b]carbazoles with various groups at 5-C and 11-C the Joule approach may be used but apart from this there remains a requirement for a route to other derivatives particularly those stipulated by the Hantsch-Topliss analysis which has been referred to previously.

In the mid-seventies chemists at Bath, pioneered a versatile synthesis which also employs mild conditions.[44] Here the



ROUTE 11

chloroethylpyridine (52) was condensed with indolylmagnesium-bromide affording the "1:1 product" (53). Drawing on the experience in the earlier syntheses of 4-acetylpyridines,[11,12] the pyridylindolylethane (53) was efficiently converted to the nitrile (54) and this on treatment with methyllithium followed by hydrolysis of the product imine gave ellipticine in high yield.

The yield limiting step to the whole sequence was the Grignard condensation. Many man-hours have been spent on attempting to optimise and improve the conditions of this reaction,

all without much success. Since the subsequent chemical manipulations work in high yield efforts to obtain the compound (53) in high yield adapting different approaches have been made.[45]

The synthetic work undertaken and discussed in this thesis was aimed at obtaining compounds of the type (53) in a versatile high yielding reaction sequence.

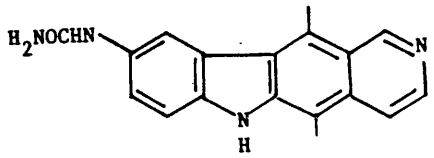
RESULTS AND DISCUSSION

DISCUSSION

SYNTHESIS OF 9-AMINOELLIPTICINE

The high anti-cancer activity of 9-hydroxyellipticine against experimental tumours justifies the requirement to synthesise aminoellipticine and to convert it into the carbamate derivative (55). Such work would complete the suggestions of the Topliss-Hantsch approach to optimal activity in this series (see p. 8).

To this end we repeated Webb's[30] synthesis (route 3, p.14) of 9-amino-ellipticine with the intentions of optimising yields and then transforming the amine into a variety of derivatives including the urea (55).



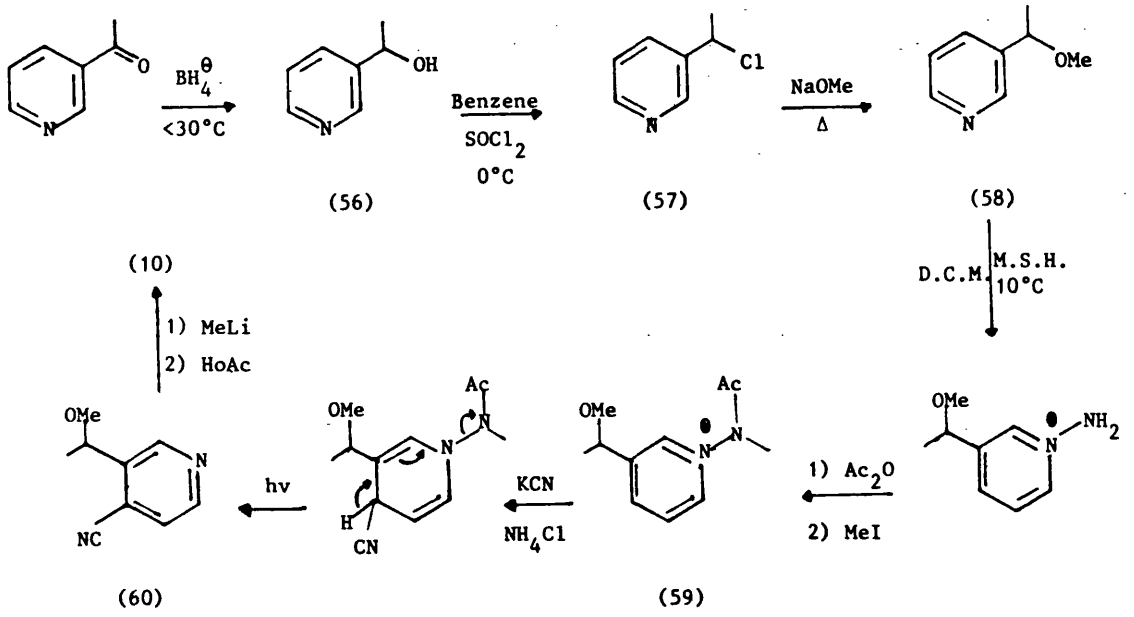
(55)

The first target for this work was the 4-acetylpyridine (10) which was prepared via the 4-cyanopyridine (60) as shown in Scheme 1 below. Details of this preparation have already been published and the sequence is far superior in overall yield to the alternative construction which takes advantage of a Wibaut-Arens reductive acylation of 3-(1-methoxyethyl)pyridine (58) despite the fact that more steps are involved.

We now find that the following conditions which differ only slightly from the original, afford the best yields. 3-Acetylpyridine is reduced at < 30°C with excess sodium-borohydride in ethanol to give the hydroxyethylpyridine (56) in 97% yield.

The alcohol is then treated with one and a half molar excess of thionylchloride at 0°C to yield the hydrochloride salt of (57) which on cautious basification at a temperature not exceeding 5°C, followed by ether extraction, gives the chloroethylpyridine (57)

in 90% yield. The product, a light yellow oil, is boiled with methanol containing one molar equivalent of sodium methoxide for five hours, and on work up this gives a brown oil, vacuum distillation of which affords a colourless oil characterised as the methoxyethylpyridine (58).



Scheme 1

This compound is next aminated and the product N-acetylated and N-methylated by a technique which has been used often in these laboratories. Treatment of the pyridine (58) with O-mesitylene-sulphonylhydroxylamine in dichloromethane gave the corresponding N-amino salt which on treatment with acetic anhydride and rapid work up for bases afforded the N-acetyl derivative. This, without further purification, was methylated by heating under reflux with methyliodide to give the methiodide (59).

The methiodide thus obtained was treated with aqueous potassium cyanide, buffered with ammonium chloride, and irradiated with soft U.V. light which serves to oxidise the intermediate dihydropyridine to the nitrile (60), probably by initial homolysis

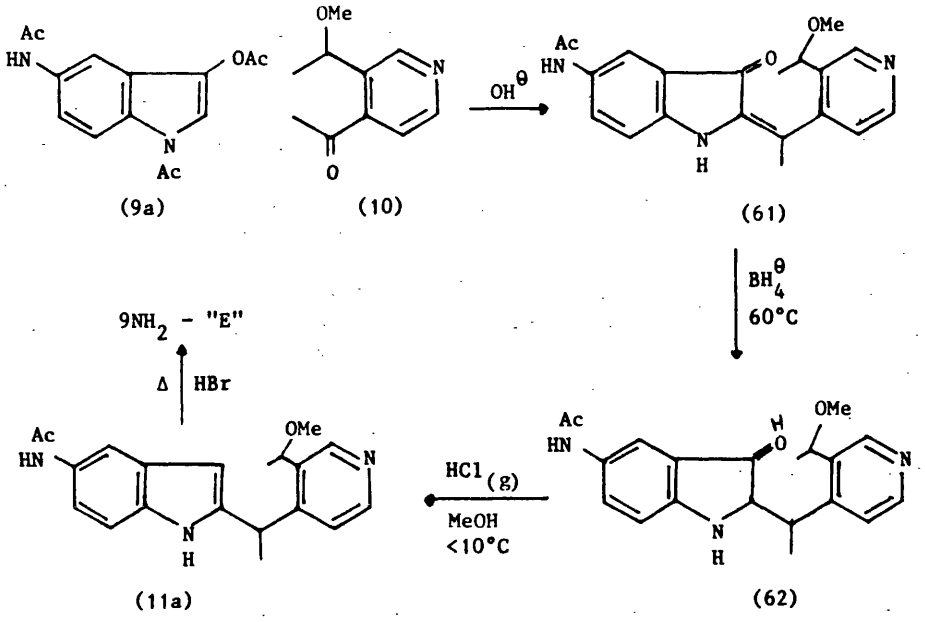
of the N-N bond.

It has been our general experience that when the original pyridine to be aminated bears a bulky 3-substituent the products of further elaboration tend to be crystalline solids which are then easily handled and purified. However, when there is a relatively simple substituent, as here, viscous oils are encountered which tend to decrease the efficiency of the procedure.[45,46]

The nitrile was reacted with methyllithium in the cold to give the corresponding imine which was easily hydrolysed on treatment with hot aqueous acetic acid to afford the required 4-acetylpyridine (10) in high yield.

5-Acetamido-1,3-diacetylindoxyl (supplied by D.M. Dolman[47]) was then condensed with the 4-acetylpyridine in the presence of sodium hydroxide to give a mixture of the E- and Z-isomers of the enone (61) as a deep red coloured solid. This condensation is very efficient providing that atmospheric oxygen is removed from reagents and solvents prior to use and that an air free atmosphere is maintained during the reaction itself. (If these elementary precautions are not observed the product is contaminated with the corresponding indigotin.) The isomeric enones were not separated but reduced in hot ethanol solution using sodium borohydride as a reductant. On work up the alcohol (62) was obtained as a mixture of diastereoisomers and this was subsequently dehydrated to the required indole (11a) by the action of hydrogen chloride in methanol (Scheme 2).

Unfortunately the indole (11a) did not crystallise, although it was chromatographed several times and it was clear that we were going to be unable to separate the diastereomeric forms without resorting to very careful work. The next step in the synthesis is



Scheme 2

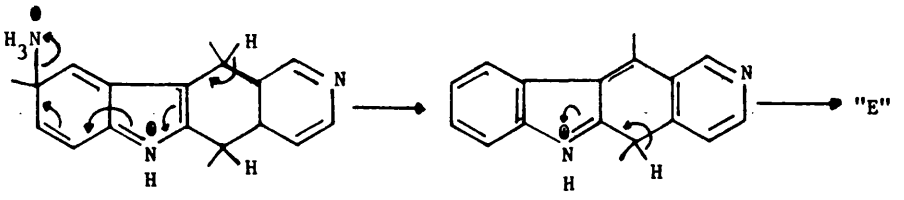
effectively the last one since previous work has shown that when indoles of this type are treated with hydrogenbromide cyclisation and oxidation to the appropriate pyrido[4,3-b]-carbazole occur consecutively. Since ellipticines do not contain any chiral centres we were not unduly worried about the problem of separation of the diastereomers and pressed ahead with the mixture to the last reaction.

The oil was heated with 60% hydrobromic acid at reflux for ten hours and the yellow solid which formed on cooling was collected, dissolved in water and the solution basified. The solid product was then filtered off and crystallised from benzene. Comparison of this material with authentic 9-aminoellipticine verified that we had made the required compound alright, but unfortunately the yield overall was abysmal.

In retrospect it might have been better to have purified the diastereomeric mixtures as the synthesis progressed, although the effort would have detracted from the utility of the approach.

We again encountered in the last step a major loss of product through deamination, for in addition to 9-aminoellipticine a considerable amount of ellipticine itself was also obtained by work up of the mother liquor from which 9-aminoellipticine bromide salt separated.

This deamination is an interesting process which may operate through protonation of the necessary dihydropyrido[4,3-b]-carbazole intermediate. As the conjugate acid (12a) aromatisation is facilitated probably as shown in (12a → 13a).



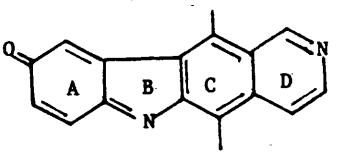
(12a) (13a)

In support of this it has been established that if the 9-substituent is able to leave with its electron pair, as is the case with halogeno and amino groups etc., then the aromatisation of the tetracycle and loss of the group at C-9 is the major product forming reaction. But when the substituent (e.g. phenyl) is not able to form an anion, cyclisation and aromatisation is accomplised without elimination of the group at the 9-position.

Altogether we were very disappointed by the results. Since unless the synthesis was to be repeated on a very large scale we would be unable to effect all the convertions we wished to do and moreover we now had insufficient 9-aminoellipticine from our first attempt even to prepare the carbamate derivative in an amount acceptable to the pharmacologists who wished to test it.

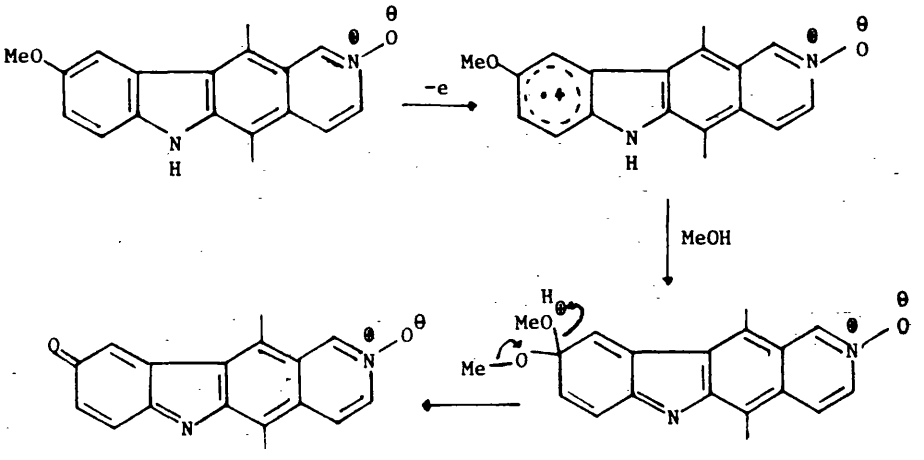
One of the other reactions we were hoping to do was an oxidation of 9-aminoellipticine to the azaquinone (63), using as

our precedent the oxidation of aniline to 1,4-benzoquinone. At this point in time the requirement to form this compound took precedence over our other aims since Paoletti[48a] had postulated this azaquinone as the actual species which intercalates between the base pairs of D.N.A. His suggestion being that in the cell ellipticine is oxidised first to 9-hydroxyellipticine then to the azaquinone which chemically bonds to the bases with concomitant aromatisation of ring A.



(63)

Since we failed in our attempt to synthesise a reasonable stock of 9-aminoellipticine, we thought that we might attempt the synthesis of 9-methoxyellipticine and either demethylate it and then oxidise the product[48] or oxidise it directly by anodic techniques. In the latter case we envisaged protecting the



(63a) (64)

pyridine nitrogen atom by, for example, N-oxide formation and then effecting oxidation in methanol solution. In simple anisoles E.S.R. studies of the corresponding radical cation show that the ipso positions have a high degree of electron density and react with solvent methanol to yield acetals. Our thoughts were that the radical cation of 9-methoxyellipticine might behave

similarly and form the acetal (64) which should readily breakdown *in vivo* to the required azaquinone. Should the methoxy group enter elsewhere in the system (or the radical cations dimerise) this would also lead to a new product so that all in all this work seemed to promise some interesting chemistry.

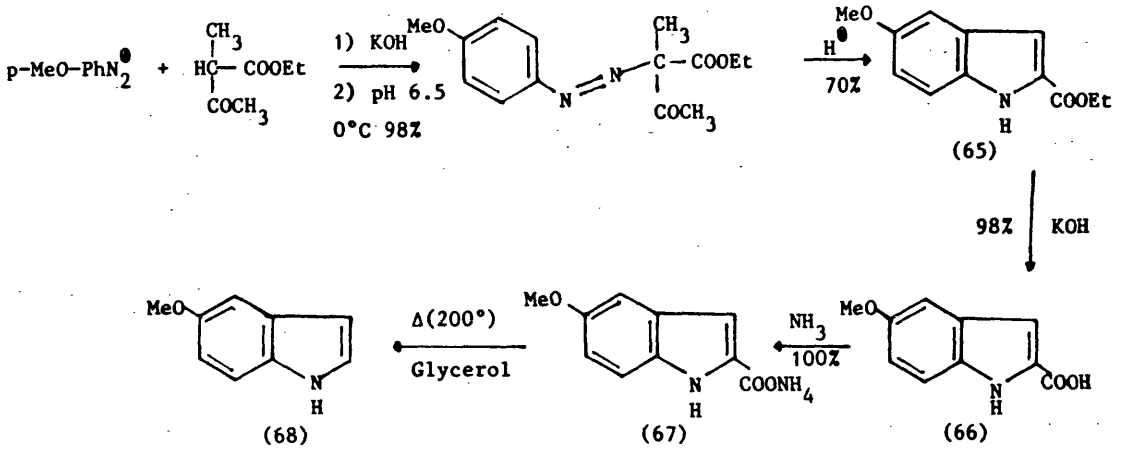
Attempted synthesis of 9-methoxyellipticine

Thus we set about the process of synthesising a quantity of 9-methoxyellipticine. Although Dalton *et al.*,[36] synthesised 9-methoxyellipticine via the route 6 (p. 17) and subsequently French chemists have also used the same route, we decided to proceed via our own route 11 (p. 23) utilizing all the expertise available at Bath.

One must point out that this was not an arbitary decision but arrived at primarily because the Vilsmeier formylation of dimethylcarbazoles is not regioselective and thus the separation of isomeric products midway through the sequence was in prospect.

The first objective then was to prepare a stock of 5-methoxyindole. Perkin and Blaikie[49] initially synthesised methoxyindoles by the thermal decarboxylation of the corresponding indole-2-carboxylic acids, but the starting materials are themselves not very accessible and the yields in the final step are poor. Later Heath-Brown and Philpott[50] improved the productivity of this approach by forming the indole-2-carboxylic acids via the Japp-Klingeman reaction then further simplified matters by decarboxylating them by heating in quinoline over copper chromite catalyst. However, by far the best method of decarboxylation is due to Marchant and his co-workers;[51] here the ammonium salt of the indole carboxylic acid is heated in glycerol.

We used a composite of these approaches, i.e. a Japp-Klingeman reaction to 5-methoxyindole-2-carboxylic acid and then thermolysis of its ammonium salt (Scheme 3). Ethylacetoacetate



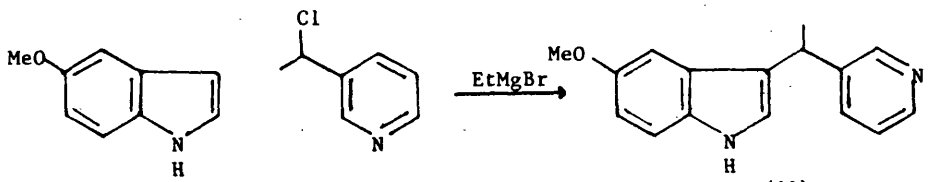
Scheme 3

was c-methylated using sodium ethoxide and methyliodide to give the α-methylethylacetoacetate which was combined with the diazonium salt derived from 4-anisidine previously treated with potasium hydroxide.

Dichloromethane extraction afforded the hydrazone in 98% yield as a viscous red oil and this was cyclised to the indole-2-ester (65) by treatment with ethanolic hydrochloric acid. The ester was hydrolysed to the corresponding acid by boiling with a three molar excess potasium hydroxide solution and converted into the ammonium salt (67) by the action of ammonia, followed by the removal of solvent water under reduced pressure. Decarboxylation was then effected by stirring this salt in glycerol maintained at a temperature of 200°C. On work up 5-methoxyindole (68) was obtained in 90% yield.

This hybrid synthesis is very effective and can be used on a large scale with an overall yield of more than 65%. Our

achievement here in finding a high yielding route to the indole was more than overshadowed by the disappointing yield of the subsequent Grignard reaction with the chloroethylpyridine (52) (route 11, p.23).



(69)

Accepting that there is a long standing problem with this type of reaction we set about attempting to overcome it. Initially it was apparent that the indolyl Grignard reagent tended to separate out from the traditional solvent-diethylether, and obviously a better medium was required. In related work Joule and his colleagues[52] have recently added a small quantity of dichloromethane to facilitate a more homogeneous system and with these in mind we carried out a series of reactions to optimise the conditions. The results of which are summarised in Table 3.

TABLE 3

Solvent	Reaction Time (days)	Temperature (°C)	% Yield of Solid (m/e 252)
Ether	1, 2, 14	0 → 20(R.T.)	6%
Ether/D.C.M.	1, 2, 14	0 → R.T.	~6-7%
Ether/T.H.F.	1, 2, 14	0 → R.T.	~6-7%
T.H.F.	2	0 → R.T.	~30%
T.H.F.	2	60 → R.T.	~30%

Although the P.M.R. spectrum was unsatisfactory the U.V. spectrum

of the solid product obtained from these reactions compared well with an authentic sample of the unsubstituted indole and mass spectrometric analysis indicated the presence of the molecular ion at m/e 252, which is that expected for the required compound (69).

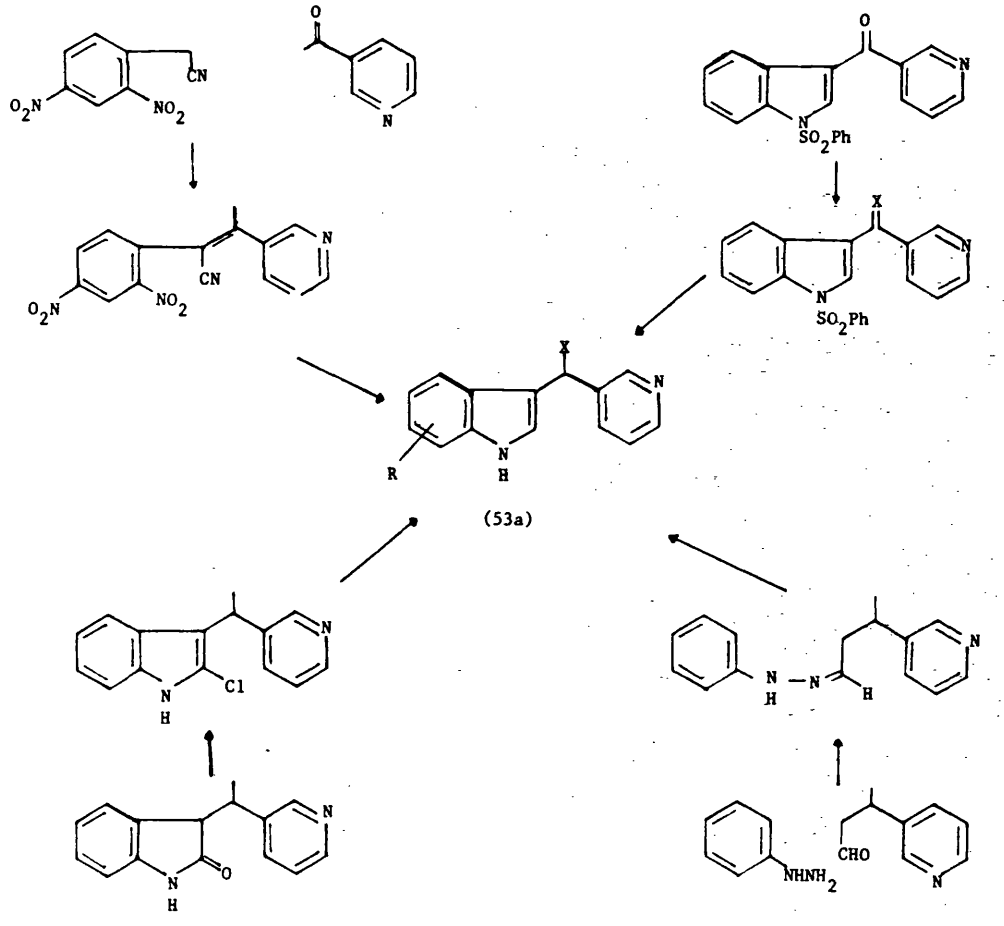
The addition of 5-methoxyindole to the ethylmagnesium-bromide in diethylether always gave a very thick precipitate/gum, which hindered mechanical stirring, but a 10:1 mixture of diethylether:dichloromethane or tetrahydrofuran afforded a suspension. Unfortunately the yield of product from the reaction remained at 6-7%.

The word "yield" is used in this context to the isolable solid that had a molecular weight of 252 and the characteristic U.V. spectrum of the required pyridylethylindole, but we could not crystallise this material and moreover the P.M.R. spectrum showed only broad unresolved signals. The sharp signal obtained for tetramethylsilane, used as internal standard in these measurements showed clearly that the poor quality of the spectra was not due to the presence of paramagnetic ions but organic impurities.

Sadly chromatography, extraction into hot petrol, ether, etc., did nothing to improve the purity of these samples, and so we abonded the use of diethylether solvent mixtures and turned instead to tetrahydrofuran.

This solvent dissolves the Grignard reagent completely and this reacted with the chloroethylpyridine exothermally to afford a solid product which again was a mixture mainly comprised of the required compound (69) but which was difficult to purify. Since 5-methoxyindole is obviously less acidic than indole itself

we wondered if the formation of the Grignard reagent was proceeding to completion and at the same time we began to wonder about the authenticity of the product which we had obtained. Concurrently work was also proceeding with 6-methoxyindole[53] and the same type of results were emerging much to the discomfort of my colleague at the bench. However, one final repetition of the reaction with the 5-methoxyindole gave a small quantity of a much cleaner product. Chromatography on silica and two crystallisations afforded a pure sample of the pyridylethylindole (69) for which unequivocal spectroscopic and analytical data were obtained. This experience was rather sobering and convinced us that something must be done to expedite a reasonably simple yet high yielding route to



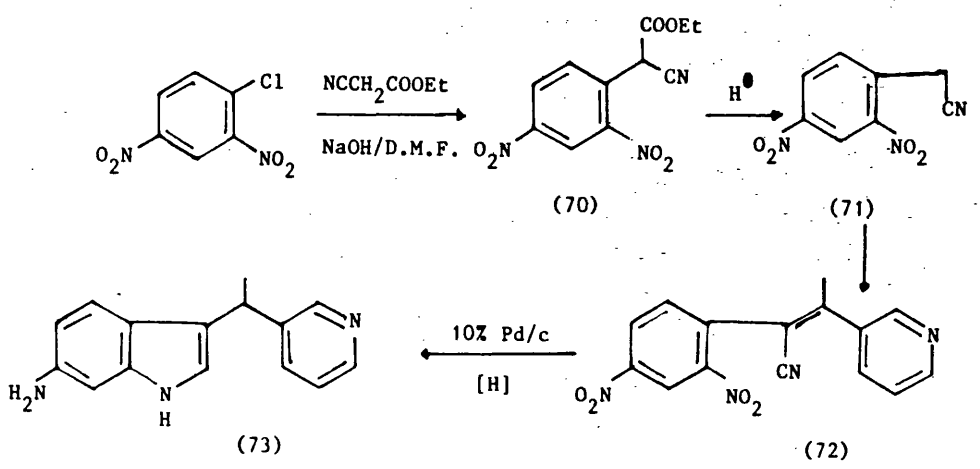
Projected syntheses to pyridylethylindoles

pyridylethylindoles.

We knew that once the pyridylethylindole was formed the other steps to the tetracycle would work well since several related syntheses of this type had been done before and so we decided upon a number of possible ways around the initial problem. These are outlined above and we started work on them concurrently in the hope of achieving a positive solution by one method or another.

Synthesis of 2,4-dinitrophenylacetonitrile and attempted condensations

It is well known that 2-nitrophenylacetonitriles can be reduced and cyclised to indoles[54,55] and one approach which we considered was to react 3-acetylpyridine with 2-nitrophenylacetonitrile, followed by reduction and cyclisation to the corresponding indole. Some initial studies had already been conducted along these lines by Schinazi[56] but these were inconclusive. In order to test the viability of the scheme we selected readily available 2,4-dinitrophenylacetonitrile as starting material which we thought would react well with the ketone under basic conditions.



Scheme 4

We prepared this starting material from 2,4-dinitrochlorobenzene and monosodio ethylcyanoacetate, followed by hydrolysis and decarboxylation of the product ester (70) by heating in 10% aqueous hydrochloric acid solution.[57,58]

Walker observed that the corresponding 4,5-dimethoxy-2-nitrophenylacetonitrile underwent Knovenagel type condensations with benzaldehyde, and thus we were encouraged to attempt a similar condensation using 3-acetylpyridine and piperidine. However, no product was formed and we concluded that perhaps the conditions were insufficiently vigorous, particularly since we know that 3-acetylpyridine is only a weak electrophile.[59] Some examples of the subsequent reaction attempts then employed are shown in table 4.

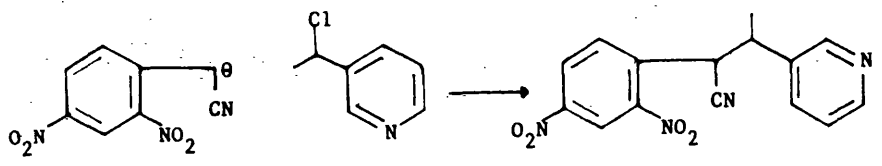
TABLE 4

Reaction conditions for attempted condensation of 2,4-dinitrophenylacetonitrile with 3-acetylpyridine

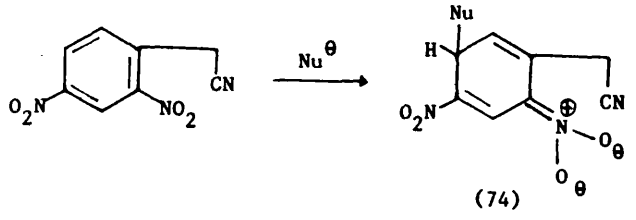
(i) piperidine, ethanol at reflux.
(ii) ethanolic hydrochloric acid at reflux.
(iii) sodium hydroxide in dimethylformamide.
(iv) Dean-Stark apparatus - benzene solvent catalysts used
1) 4-toluenesulphonic acid
2) piperidine
3) pyrrolidine
4) acetic acid/ammonium acetate

No tangible products were isolated, however, yet we were fairly certain that the phenylacetonitrile was reacting with the bases employed since deep red solutions were formed as soon as the reagents were added.

We now changed from 3-acetylpyridine to 3-chloroethyl-pyridine which has previously been reacted with several types of nucleophile (including, of course, the Grignard reagents) and in our first attempt we used sodium ethoxide in ethanol to



generate the necessary anion. This gave a tar and at this point we were concerned that Meisenheimer complexes of the type (74) were forming. Clearly this might explain our lack of success



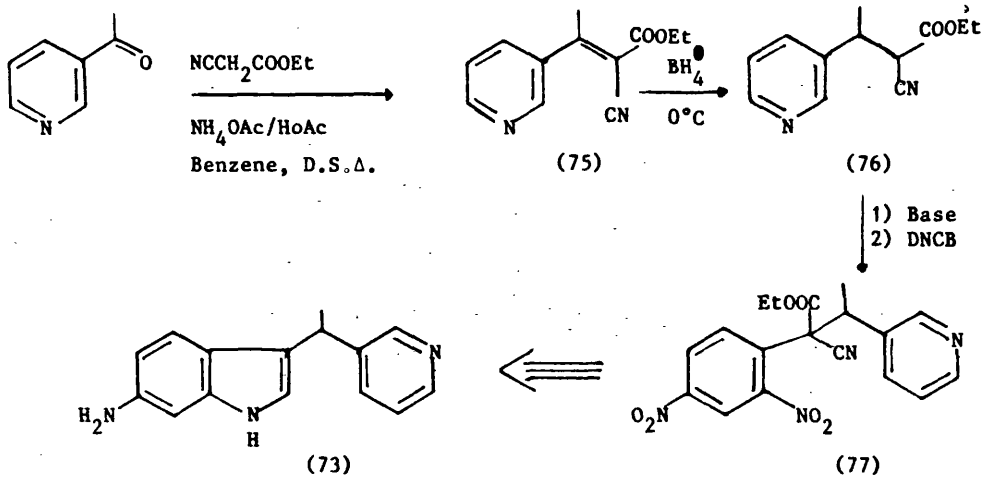
(74)

and account for the deep red coloured solutions that we had obtained.

A solution to this problem might be to employ a hindered base and consequently we tried a number of these but all our attempts ended in similar failures and red solutions were once again produced. Furthermore we were unable to combine the nitrile with pyridine-3-aldehyde which is known to be quite a good electrophile under our reaction conditions.

The aldehyde, nitrile and pyrrolidine in dry benzene were heated at reflux using a Dean-Stark apparatus for six hours. Base work up afforded only the starting pyridine aldehyde and there was no evidence of water being generated.

Disappointed in our efforts we projected a new sytnhesis to the same compound (73) as shown in Scheme 5.



Scheme 5

Synthesis of ethyl-3-(3'-pyridyl)-2-cyanobutanoate and its attempted condensations

Initially we preformed the anion of cyanoacetate ester by treatment with sodium ethoxide[60] and attempted to react it with 3-acetylpyridine, but on work up for bases, only the starting pyridine was obtained.

In the 1940's Cope et al.[61,62] condensed ethylcyanoacetate with a variety of carbonyl compounds in the presence of ammonium acetate and glacial acetic acid in dry benzene. Cragoe et al.[63] improved the yield of this type of condensation by the portionwise addition of ammonium acetate at hourly intervals throughout the reaction. In this way it is claimed that fresh catalyst is always available rather than its destruction by decomposition into acetamide within the early part of the reaction.

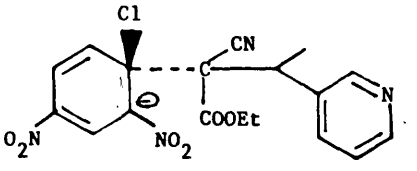
Thus 3-acetylpyridine, glacial acetic acid, ethylcyanoacetate in dry benzene were heated at reflux and ammonium acetate was added in small portions at four hourly intervals. On work up

for bases an oil was obtained. The infrared spectrum of this product showed a cyanide stretching band at νmax 2210 cm^{-1} and an ester carbonyl absorption band at ν_{max} 1715 cm^{-1}, in addition there was a second carbonyl absorption at ν_{max} 1695 cm^{-1} which is exhibited by 3-acetylpyridine. A thin layer chromatography analysis confirmed that unreacted 3-acetylpyridine was present together with a 'new' component. When this oil was distilled under reduced pressure the starting ketone was obtained as an early fraction leaving a residue consisting mainly of the alkylidene ester (75), the structure of which was confirmed by spectroscopy.

As expected the compound could be reduced with sodium-borohydride[64] to the corresponding alkane (76) and after a few trial runs using ethanol, or isopropanol, as solvents and varying the molar quanitities of reductant, substrate and reaction temperaure we arrived at the optimum conditions for this reduction, namely one molar equivalent of sodium-borohydride at 0°C in isopropanol. On work up for bases the saturated pyridylcyanoacetic ester (76) was obtained in 90% yield. The next step of our synthesis was to effect the displacement of the chlorine atom on dinitrochlorobenzene with the anion of this compound. Initially we tried sodium-hydroxide in dimethylformamide as reagent to form the anion and then added the dinitrochlorobenzene but on work up for bases the cyanoacetic ester was returned unchanged. Thus the reaction was repeated at higher temperatures and longer times, but with the same result.

It is likely that in these reactions hydroxide ions preferentially displace the chlorine atom of the nitrochloro-

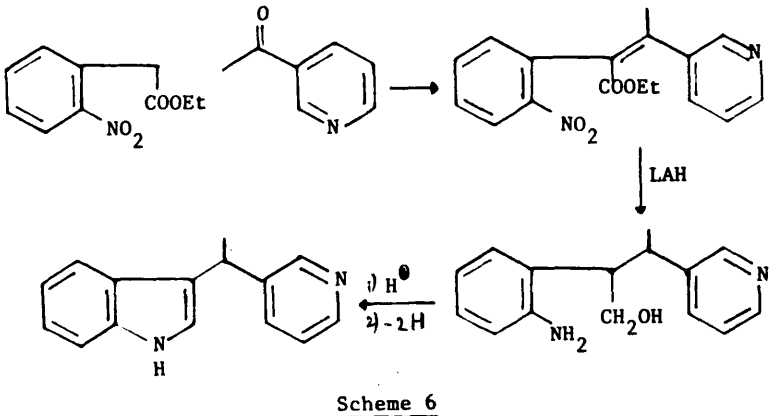
benzene and assuming that non-aqueous conditions and more rigorous control of the available nucleophiles were required, we next employed lithiumdiisopropylamide, preforming the anion of the ester before the addition of the electrophiles. This also failed as did reverse addition experiments. We can only explain these last failures by suggesting that the size of the anion of the pyridylcyanoacetate precluded the formation of a suitable reaction intermediate but nevertheless we attempted one last experiment using sodiumhydride as base.



(78)

We are sure that the required anion formed since the evolution of hydrogen gas was noted from a solution of the cyanoester, but once again after addition of the nitrochlorobenzene and work up for bases only the pyridylcyanoacetate was returned.

Unsuccessful in our efforts to obtain the compound (73) in this manner we resorted to yet another approach to compounds of the type (53) as shown in Scheme 6.



Scheme 6

Attempted condensations of 2-nitrophenylacetate with 3-acetylpyridine

Commercial 2-nitrophenylacetic acid was esterified employing Williamson conditions. The ethyl ester thus obtained, and 3-acetylpyridine were heated at reflux in ethanolic hydrochloric acid in an attempt to induce an acid catalysed condensation but work up for bases gave only unreacted 3-acetylpyridine.

Having tried two unsuccessful Knovenagel type condensations with 3-acetylpyridine using piperidine and pyrrolidine respectively as basic catalysts with the same substrate, our attention was focused on reacting the 2-nitrophenylacetate with chloroethylpyridine.

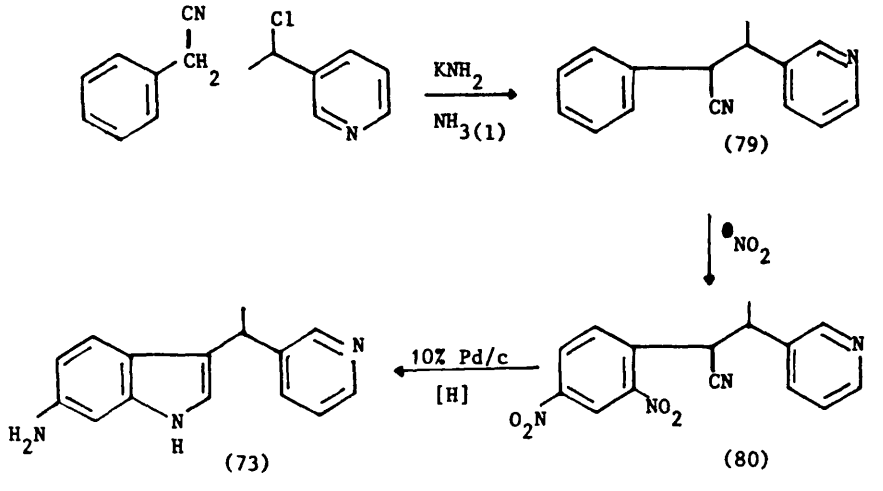
In the mid 1950's Hauser et al.[65] carried out a series of alkylation reactions of phenylacetic acid and phenylacetonitrile using sodium amide in liquid ammonia. We attempted to condense the 2-nitrophenylacetate with chloroethylpyridine under similar reaction conditions. Sodium amide was prepared in situ by the addition of finely cut sodium slices to liquid ammonia. To the resulting grey coloured solution 2-nitrophenylacetic acid was added and, after an interval, the chloroethylpyridine was introduced. Stirring was continued until all the ammonia had evaporated, then the reaction mixture was worked up for bases to afford only some unchanged chloroethylpyridine. The nitrophenylacetate was not recovered, but a resinous solid was obtained from the acid insoluble fraction.

Neither the use of sodium ethoxide, nor of lithiumdiisopropylamide, offered any improvement in condensing 2-nitrophenylacetate with chlorothylpyridine or even benzyl chloride; and at present

we are still uncertain as to why these procedures were unproductive, although we are aware that the chloroethylpyridine may be dehydrohalogenated to 3-vinylpyridine by the action of base. The most puzzling feature is the lack of reaction between the nitroester and benzylchloride, and had time not been slipping away we might have used more reactive electrophiles in an attempt to explain these observations.

Synthesis of 2-phenyl-3-(3'-pyridyl)-butancarbonitrile & its nitration

Hauser and Brassen[66] have previously alkylated phenylacetonitrile with α-phenylethylchloride in 99% yield. This prompted us to attempt the condensation of phenylacetonitrile

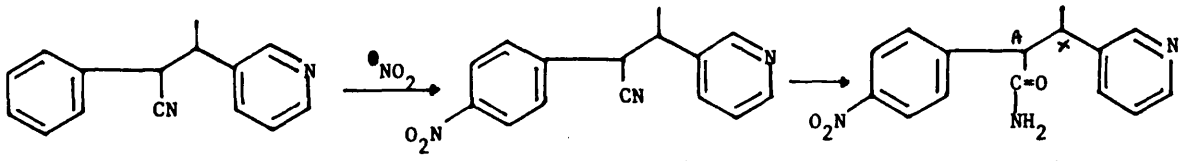


Scheme 7

with chloroethylpyridine following Hauser's procedure. Success or failure in this experiment might clarify the problem and decide whether anion formation from the nitrophenylacetonitrile or the decomposition of the chloroethylpyridine was causing us so much difficulty. If this alkylation proved successful we were going to nitrate the product and proceed as shown in Scheme 7. Potassium amide was prepared in situ and to the ensuing grey suspension in ammonia, phenylacetonitrile was added. After

fifteen minutes of vigorous stirring, chloroethylpyridine was introduced into this mixture and the combination then stirred until all the solvent ammonia had evaporated. On work up for bases a white solid was obtained. Spectroscopic analysis proved it to be the condensed product (79). The success of this reaction was surprising in view of our past experiences. Here we have a less stabilised anion and one might have expected a less formidable situation, however, perhaps with nitro groups the anion is too stable; and the competing dehydrohalogenation reaction is now kinetically dominant. One can hardly invoke the formation of Meisenheimer complexes as an explanation with just one nitro group present in the substrate. Having been successful at last we now attempted a nitration of the product using concentrated nitric and sulphuric acids at 0°C. This afforded the 4-mononitro derivative (81). Attempts to nitrate the mononitro derviative further on to the dinitro compound (80) using the same conditions was not successful, and we had to employ more severe conditions which regretably gave intractrable tarry products. When the nitration was carried out using methylnitrate it gave a mixture of mononitro derivative and a small amount of white solid.

Spectroscopic examination of the compound showed the absence of a cyanide group but in the infrared spectrum the presence of strong absorption bands at 1680 cm^{-1} and at 1595 cm^{-1} (overlapping the pyridine ring carbon stretching) indicated that the cyanide function had been hydrolysed to an amide group. The P.M.R. spectrum confirmed these conclusions and showed a broad peak at 6.7 ppm which can be eliminated when deuterium

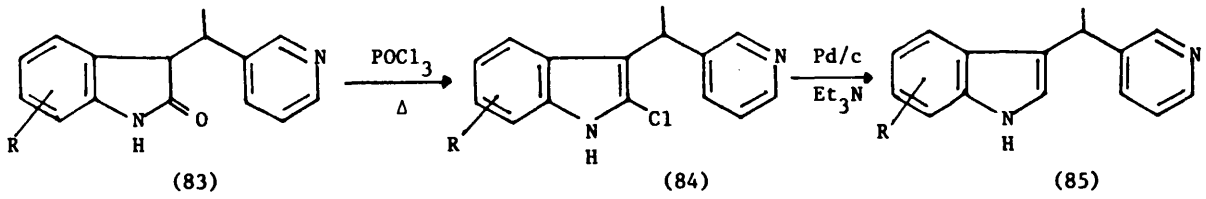


(79) (81) (82)

oxide is added. Additionally the methine proton (A) adjacent to the carbonyl group resonates as a doublet at 3.9 ppm coupled to the other methylene proton labelled (X) in formula (82) which appears as a multiplet at 3.5 ppm. In the spectrum of the starting material (81) the doublet appears at 4.9 ppm and the multiplet at 3.5 ppm. The shifting of the doublet by one ppm downfield in the product is a classic case of anisotropic effect of the carbonyl group which causes a deshielding effect on the protons lying on a cone extending from the carbonyl oxygen atom. In the mass spectrum the molecular ion peak is exhibited at m/e 285 corresponding to the amide (82) and thus structural allocation is further supported by elemental analysis. The use of the acetylnitronium species which is known to give predominently 2-nitration[67] in related situations, but when applied to our substrate, reactions which involve this ion lead only to tarry products immediately forcing conditions were employed and it became apparent that the deactivation caused by mononitration deterred further reaction at the aryl ring in a controlled sense. So once more we were forced to a halt and had to begin yet another approach to our desired goal.

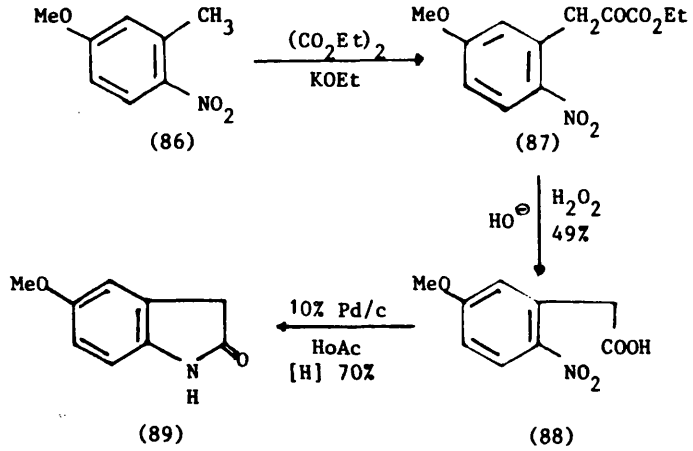
Synthesis of 3-[1-(3'-pyridyl)ethyl]-5-methoxy-2-chloroindole and attempts at dehalogenation

Kubo and Nakai have claimed recently[68] that it is possible to convert 2-chloroindoles (84) into the corresponding indoles by reduction over palladium and subsequent treatment of the products



(83) (84) (85)

with triethylamine. The necessary 2-chloro derivatives are made by the action of phosphorus oxychloride on the readily available oxindoles (83), thus providing what appears to be a simple route to pyridylethyl indoles. The parent compound (85, R=H), for example, was said to be prepared in 73% yield from the oxindole (83, R=H). Indeed Kilminster[30a] in this department has already made this oxindole in excellent yield by firstly reacting 3-acetylpyridine with oxindole and then reducing the product indolylidene derivative. Thus we visualised the reaction of 5-methoxyoxindole with 3-acetylpyridine, and its spbsequent conversion to the required pyridylethyl indole (85, R=5-MeO) to be a formality and synthesised the 5-methoxy-oxindole via the sequence shown in Scheme 8, as a preliminary to the formation of this compound.



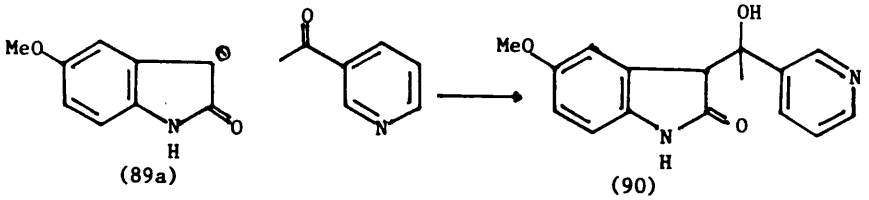
(86) (87) (88) (89)

Scheme 8

Perkin et al.,[49] in their preparation of 5-methoxyindole, condensed the nitroanisole (86) with diethyloxalate to give the pyruvic ester (87). This was cleaved on treatment with alkaline hydrogenperoxide to yield the phenylacetic acid (88) in 49% yield. We repeated this procedure and then followed the conditions described by Walker[54] and McDonald et al.,[69] for its reductive cyclisation to 5-methoxyoxindole. Our yield was 70% for this final interconversion and subsequently 6-methoxyoxindole was synthesised in our laboratory using the same technique.[70]

Having obtained 5-methoxyoxindole in this fashion we then reacted it under Kilminster's conditions with 3-acetylpyridine in the presence of pyrrolidine, but on work up for bases starting material was returned. Changing the various parameters, i.e. molar ratio of reactants, reaction temperature, catalyst concentration and the reaction time made absolutely no difference. Failure was experienced each time and similar results were obtained when the base was changed to piperidine.

Assuming the need for a stronger base, lithium diisopropyl-amide and lithiumdicyclohexylamide[71] were used to facilitate the

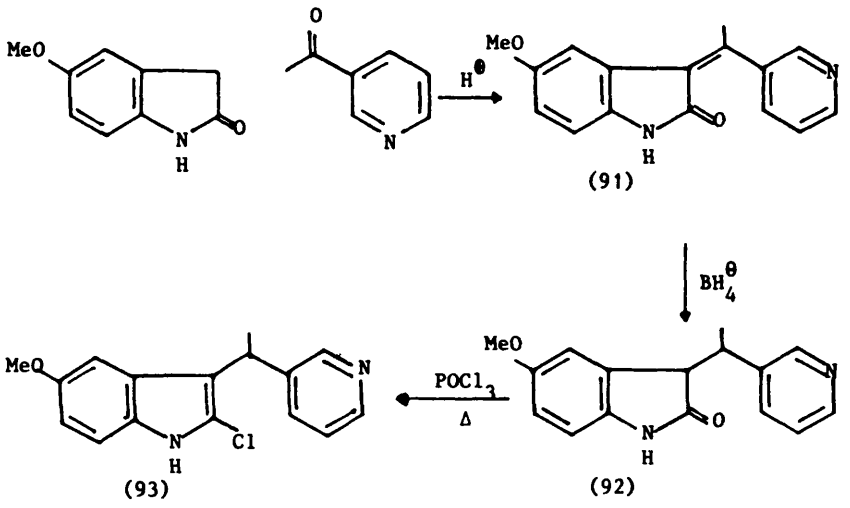


(89a) (90)

prior formation of the anion (89a) but again no reaction was observed.

At this point we wondered if we should change to an acid catalysed reaction since it appeared as if the presence of the methoxyl group was inhibiting anion formation. Accordingly, we reacted the oxindole with 3-acetylpyridine in the presence of

ethanolic hydrogenchloride and this gave the required indoxylidene (91) in 80% yield as an orange coloured solid.



Scheme 9

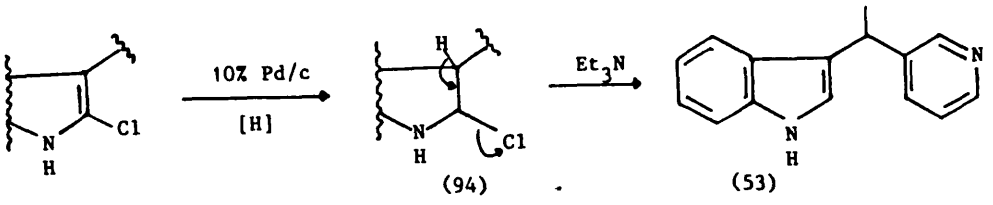
Reduction of this product with sodium borohydride gave the corresponding dihydro derivative which was then treated with phosphorus oxychloride affording the 2-chloroindole (93) in 60% yield.

A solution of the chloroindolylpyridine in ethanol was hydrogenated (80 lb/sq inch) in the presence of 10% palladium on carbon and a few drops of triethylamine. On work up only the chloroindole was returned. The hydrogen pressure, catalyst ratio and reaction time were all varied in a systematic manner without success. Eventually a gram of the chloroindole and two and a half grams of 10% palladium on carbon in ethanol was hydrogenated at (1200 lb/sq inch) over the weekend at room temperature. This time a trace of the dehalogenated pyridylethyl indole was obtained and compared by the Grignard reaction (p. 35). The conditions necessary made this sequence economically non-viable and we looked at alternative dehalogenation procedures.

At the same time we were experiencing similar problems

with the 6-methoxy isomers and it became clear that Kubo and Nakai's claims are of limited justification. However, we considered their concepts were attractive and all that was required was an alternative technique and a number of reagent systems were tried.

It is relevant to discuss the probable mechanism by which Kubo and Nakai achieved thier reductive dehalogenation and hence explain our effort towards the same goal. It is likely that the indole is initially reduced to the indoline (94) and then the presence of the base triethylamine facilitates the dehydrohalogenation to the indole.



If this is correct then a survey of Robinson's review[72] on the reduction of indoles explains why such harsh conditions were needed for the loss of aromaticity within the indole system is a strong deterrent to reduction. It is claimed, however, that other metals, e.g. platinum or nickel (Raney), are more effective catalysts, but under vigorous conditions it is not uncommon for both indolic and pyridine rings to be reduced when present together as in the substrate (93).

Gordon Gribble and his group[73] have reduced indoles and quinolines in glacial acetic acid by the action of sodium cyanoborohydride, however, application of this technique to our compound was not successful.

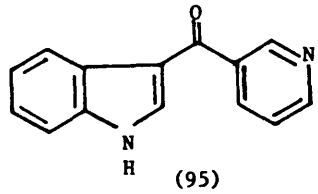
Wakametsu et al.,[74] have demonstrated the selectivity of tetra-n-butylammoniumborohydride as a reducing agent for amides

and nitriles but they have also used it to reduce indoles to the corresponding indolines. We prepared tetra-n-butylammonium-borohydride[78] and attempted to react it with the chloroindole, but again without success.

Disappointed by our lack of achievement here we turned to investigate the possibility of alkylating pyridyl indolyl ketones, but before we examined the alkoxylated compounds we sought to define the necessary conditions with the model (95).

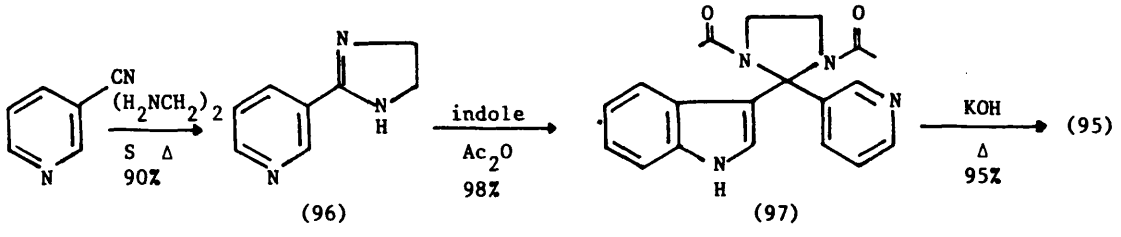
Synthesis and chemistry of 3'-(indol-3-ylformyl)pyridine

Webb[46a] reacted nicotinylchloride with indolylmagnesium bromide to obtain the pyridylindolyl ketone (90) in 60% yield, but the carbonyl frequency of this compound occurs at 1595 cm^{-1} in the infrared spectrum which



(95)

indicates that it is more of an vinylogus amide than a ketone. We reasoned that if the NH group were converted into a benzene-sulphonamide unit this vinylogy should be inhibited and indeed when this derivation is carried out the carbonyl frequency of the product is observed at 1620 cm^{-1}. Although this is still "low" we hoped that this compound might now show enough ketonic properties to react with alkylating agents and hence provide a route to pyridylethyl indoles.



(96) (97)

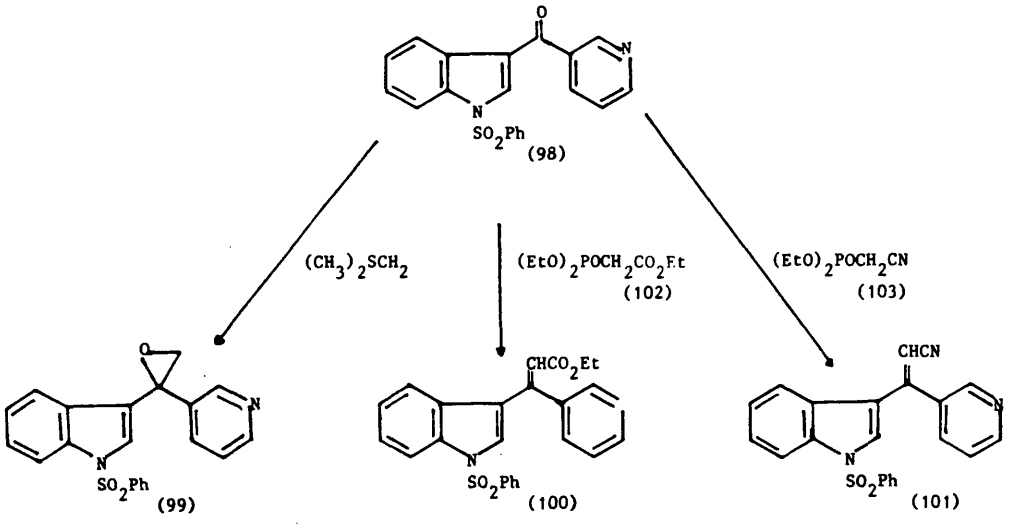
Although the yield of the reaction between indolylmagnesium bromide and nicotinyl chloride was relatively good for the

unsubstituted case our earlier experience with methoxyindolyl Grignard reactions caused us to consider alternative constructions. Fortunately we were able to follow a literature method used to acylate indoles,[76] and modify it to the system at hand. This method involves the prior construction of an imidazole which upon N-acetylation forms an excellent electrophile. When we prepared the imidazole (96) and reacted with indole in acetic anhydride we were gratified to obtain the intermediate product (97) in excellent yield. Alkaline hydrolysis then lead to the "ketone" (95) again in a very productive step (95%). We also found that a similar sequence with 5-methoxyindole gave the methoxylated analogue of (95) in an equally efficient manner, and there is no doubt that this is the method of choice in this series avoiding the requirement to form nicotinyl chloride and the Grignard reaction at the same time.

Previous work has indicated that carbonyl compounds of the type (95) do not undergo simple reactions with methyllithium, instead of one component products complex mixtures result, furthermore simple Wittig reactions also fail so that it was with some trepidation that we considered a series of possible elaborations of our substrate (95).

It seems likely that methyllithium attacks not only the carbonyl group but may also substitute in the pyridine nucleus, thus we wondered what might occur as a result of a reaction between the N-sulphonyl derivative (98) and dimsyl sodium especially as Sundberg has shown that similar compounds are metalated at the indolylic α-position. Our target was the epoxide (99) which could be reductively ring-opened to afford a useful intermediate for further elaboration onto a pyridylethyl indole.

The ketone (98) was reacted with dimethylsulphonium methylide[77] at -10°C in tetrahydrofuran and on work up a pale yellow solid was obtained, the P.M.R. of which indicated the presence of the epoxide unit but also several other components. Obviously the basic conditions prevailing in the reaction may cause the loss of the N-sulphonyl unit and TLC analysis showed that one constituent of the mixture was the ketone (95). The retention indices of the components in a variety of solvents were similar and since, our objective was to develop an efficient route to pyridylethyl indoles (still several steps ahead) we abonded this approach and turned instead to Wittig and Wittig-like reactions. Previously[45] Wittig conditions using reagents like triphenylmethylphosphonium iodide served only to de-N-sulphonate the indole which then no longer showed any ketonic



properties. Here one is unsure that complete reaction between the base and the phosphorus reagent occurs so that some base remains to bring about N-deprotection, and it seems likely that a similar effect is occurring in the preceeding dimsyl sodium reaction.

Thus we turned to the more reactive phosphonates (102)

and (103) which react rapidly and completely with a molar equivalent of base to afford the corresponding ylides. In this form they were then individually added to the carbonyl compound (98) and smooth interconversion into the derivatives (100) and (101) were noted.

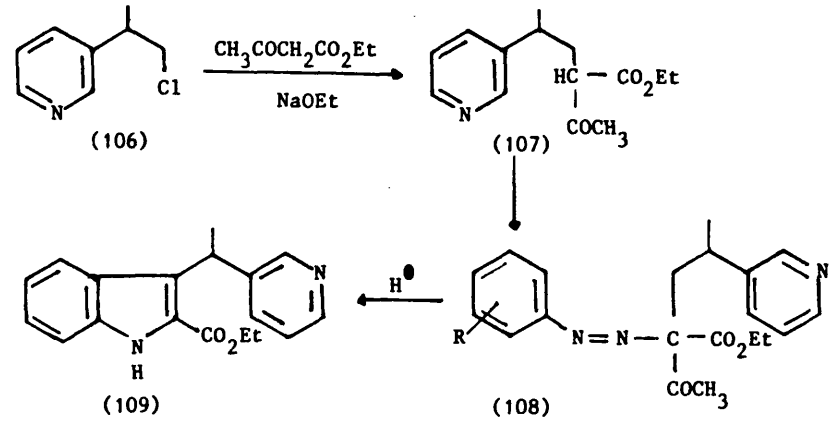
These are interesting compounds and their chemistry is currently receiving attention, but they are obviously some way remote from the original goal of pyridylethyl indoles. Clearly phosphonates such as (104) and (105) might be used to effect a synthesis of the methylene derivative, but so far we have not pusued this avenue since a simpler approach appeared to be the synthesis and subsequent indolisation of the aldehyde (117).

$(MeO)_2PSCH_3$
(104)

$[(CH_3)_2N]_2POCH_3$
(105)

Synthesis of 3-(3'-pyridyl)butanal

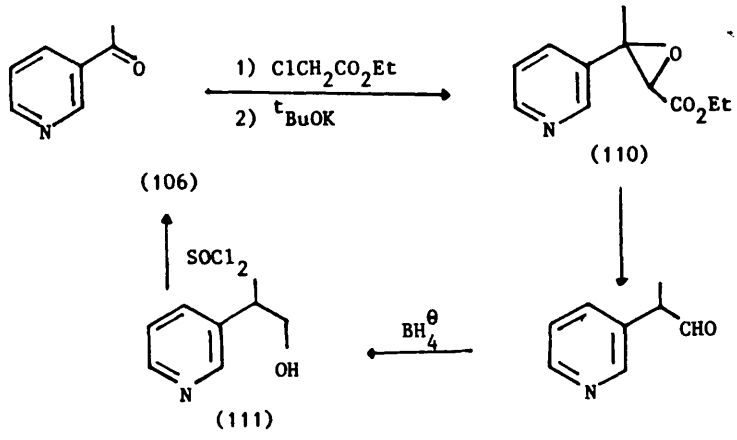
Since it is well known that ethylacetoacetate can be C-alkylated, we considered that a reaction between the pyridylpropylchloride (106) and monosodioethylacetoacetate should yield the ester (107). Under Japp-Klingemann conditions this might



Scheme 10

then form the hydrazone (108) which could be cyclised to the indole (109).

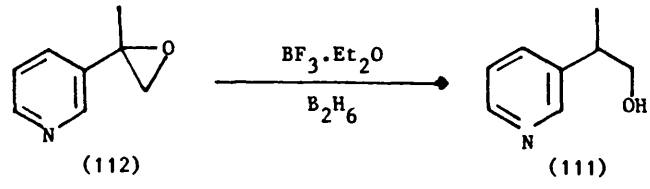
In order to prepare the necessary alkylhalide (106) the reactions of Scheme 8 were contemplated. First we envisioned a Darzen's reaction[79] upon 3-acetylpyridine to form the oxirane (110), followed by ring opening, reduction and thionyl chloride treatment of the product alcohol (111). The Darzen's reaction



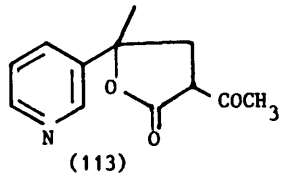
Scheme 11

has been previously carried out with 3-acetylpyridine[80] but the yeild was only 25%. In our hands the reaction failed, although a variety of different bases were used.

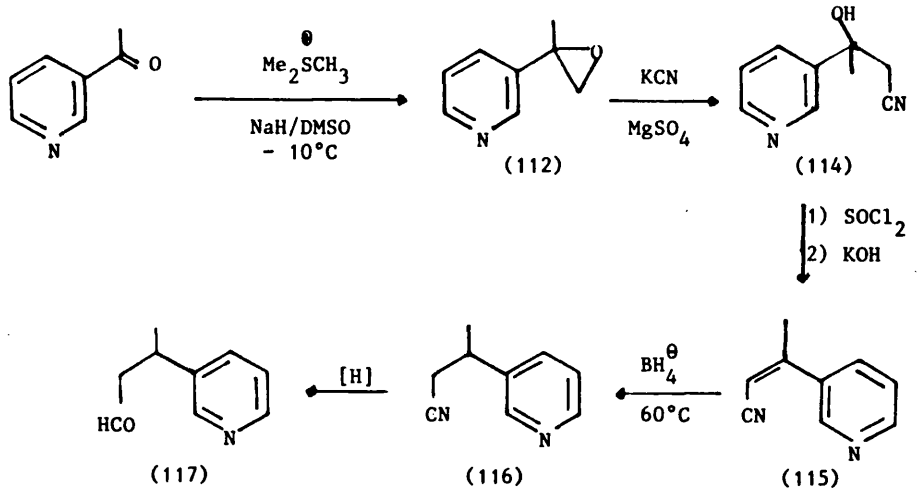
In view of this we decided to form the oxirane (112) and and to effect reductive ring opening of the epoxide using diborane



and borontrifluoroethereate to give the alcohol (111), following as our model similar cleavages by Brown and Yoon[81] who worked with the corresponding styrene oxides. At this point one might speculate upon the ring opening of the oxirane with monosodioethylacetoacetate as an alternative approach to the ester (108), but unfortunately similar reactions are known to give lactones of the type (113).[82,83] The ester (108) is still some steps away from



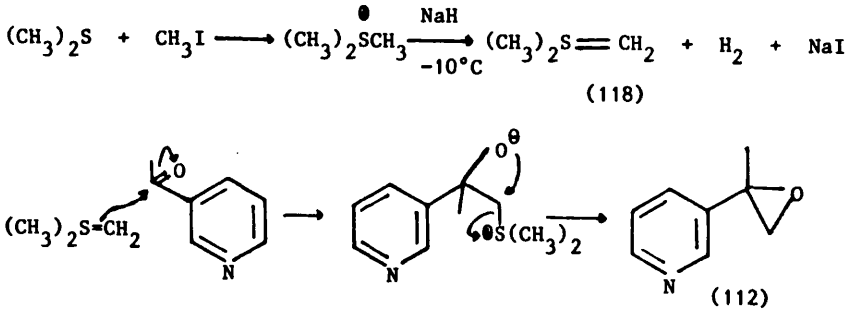
the required pyridylethyl indole, the last of which is a thermal decarboxylation of the corresponding acid. It was obvious that this prolongation of the synthesis is unnecessary since the intermediate aldehyde is the key compound. From it hydrazones can readily be made and these cyclised under Fischer conditions to pyridylethyl indoles directly.



Scheme 12

Ring fission of the oxirane, formed by the action of dimethylsulphonium methylide on 3-acetylpyridine, by the action of potassium cyanide and implementation of the steps summarised in Scheme 9 should afford this aldehyde.

Thus dimethylsulphide was reacted with methyl iodide to yield the trimethylsulphonium iodide in 98% yield.[84] The iodide was added to a cooled (-10°C) solution of dimsyl sodium in tetrahydrofuran with vigorous stirring. The temperature of the reaction mixture was maintained at -10°C throughout, since the ylide (118) rapidly decomposes as the temperature is raised. Hydrogen evolution was followed by the formation of sodium iodide which separated from the solution and as soon as the reaction appeared to be complete, 3-acetylpyridine was added in a stream, with stirring. On work up for bases the oxirane (112) was isolated in 99% yield.

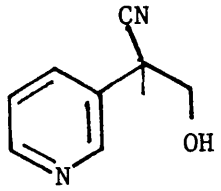


(118)

(112)

The ring opening of the oxirane with cyanide ion to give the hydroxy nitrile (114) necessitated the use of magnesium sulphate. Presumably the magnesium ion co-ordinates with the oxygen whereby facilitating cyanide ion attack at the least hindered carbon.[85,86]

Kharasch and Clapp[87] working with styrene oxides have commented that the order in which the reagents are added is very important and if the oxirane is added to the nucleophile (in their case a Grignard reagent), attack at the more hindered site occurs. There is an obvious difference between non-aqueous and aqueous conditions and we observed the exact opposite. Thus in our case addition of the oxirane (112) to magnesium sulphate in water, followed by potassium cyanide solutions affords mainly

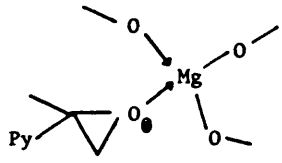


(119)

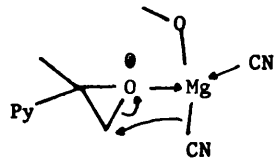
the alcohol (119), together with some of the isomer (114), whereas if solutions of magnesium sulphate and potassium cyanide are mixed and then the oxirane is added only the required alcohol (114) is formed. If magnesium ions are not present no attack by the cyanide at either position is observed.

These results are very interesting in themselves and worth further study, for example, in the case where the oxirane is

exposed to magnesium ions prior to the addition of cyanide ion it is possible that some form of co-ordination complex (120) is built up containing a magnesium atom bonded only to oxygen.



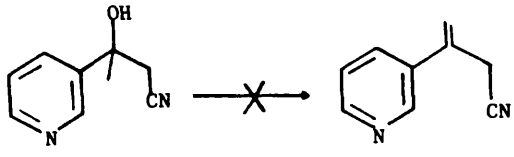
(120)



(121)

Attack by cyanide ion is now possible at either position and although the β-position is the least hindered it is the least electrophilic. When the magnesium ions and cyanide ions are present together a complex between magnesium and the oxirane (121) may contain at least one Mg-CN bond conformationally oriented so that attack at the sterically more open β-position is favoured.

Whatever the reasons behind these reactions, our immediate objectives were elsewhere and having worked out a route to the alcohol (114) it was now necessary to effect its conversion into the α,β-unsaturated nitrile (115). Of the two possible modes of dehydration the required one is the more likely since this provides the more conjugated product but unfortunately acid catalysed dehydrations of the alcohol failed, at least under moderate conditions and we assume that protonation of the pyridine nucleus is a competing reaction which tends to disfavour further attack at oxygen. In view of this we decided that base catalysed elimination reaction might serve our needs more effectively but alas our tetiary alcohol (114) could not be readily mesylated or tosylated and mixtures containing much starting material resulted.

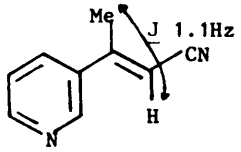


(114)

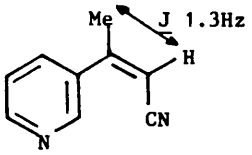
Stephen's reductions are known to be rather ineffective with

saturated aliphatic nitriles and we were not surprised when a reaction between the alcohol and stannous chloride in ether previously saturated with hydrogen chloride returned unchanged starting material.

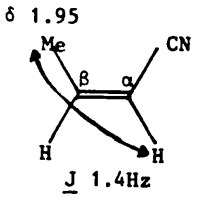
Fortunately we noted that the alcohol (114) when treated with phosphorus tribromide, followed by work up in the presence of aqueous alkali, gave an oil and on analysis of the P.M.R. spectrum of this product proved it to be a mixture of the E-(122) and Z-(123) isomers of the required alkene in molar ratio of 1:0.81. The assignments of stereochemistry rest on the following points: Reddy and Goldstein[88] have analysed in detail the chemical shift positions E- and Z- crotonylnitriles and note that when the methyl and nitrile groups are cisoid the chemical shift position of the signal due to the methyl protons is at lower field (δ_{Me} 1.95) than when the gorups are transoid (δ_{Me} 1.81). Thus proximity to nitrile group causes a small but significant deshielding effect, Δ = 0.14 ppm. For these two isomers the long range coupling constants between the α-hydrogen and the protons of the methyl group are very similar J 1.4 Hz for a trans relationship as in the Z-form and J 1.5 Hz for the cis orientation.



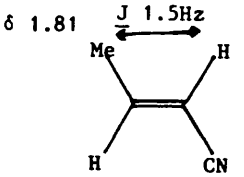
(122)



(123)



Z-

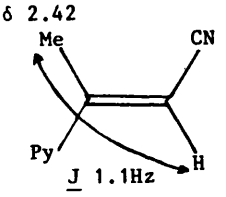


E-

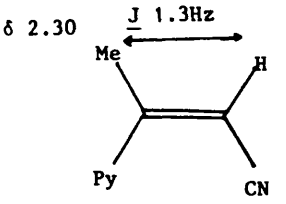
In our isomers (where incidentially the prefixes E- and Z- are opposite to that of the crotonyl derivatives) the most abundant component exhibits a signal in the P.M.R. spectrum at δ 2.42 due to the protons of a methyl group

and an olefinic resonance at δ 5.76. The minor component gives rise to similar resonances at δ 2.30 and δ 5.58. The long range coupling constants $J_{Me/H}$ are 1.3 Hz and 1.1 Hz respectively.

We conclude that the more abundant isomer in our case is the E- form in which the methyl and cyanide groups are cis and the methyl and vinyl protons are trans. Indeed this conclusion is supported by the results of nuclear Overhauser enhancement experiments. When the methyl resonance at δ 2.30 is irradiated and the corresponding olefinic proton signal at δ 5.58 is examined and enhancement of the latter signal is noted. Whereas irradiation of the methyl resonance at δ 2.42 causes no change in the intensity of the hydrogen resonance at δ 5.76 to which it is coupled. The ratio of intensities of the two vinylic resonances are 1:0.81 (average of five runs) in the latter case and also in the unirradiated spectrum. This is changed to 1;0.96 when the δ 2.30 resonance is selected for irradiation.



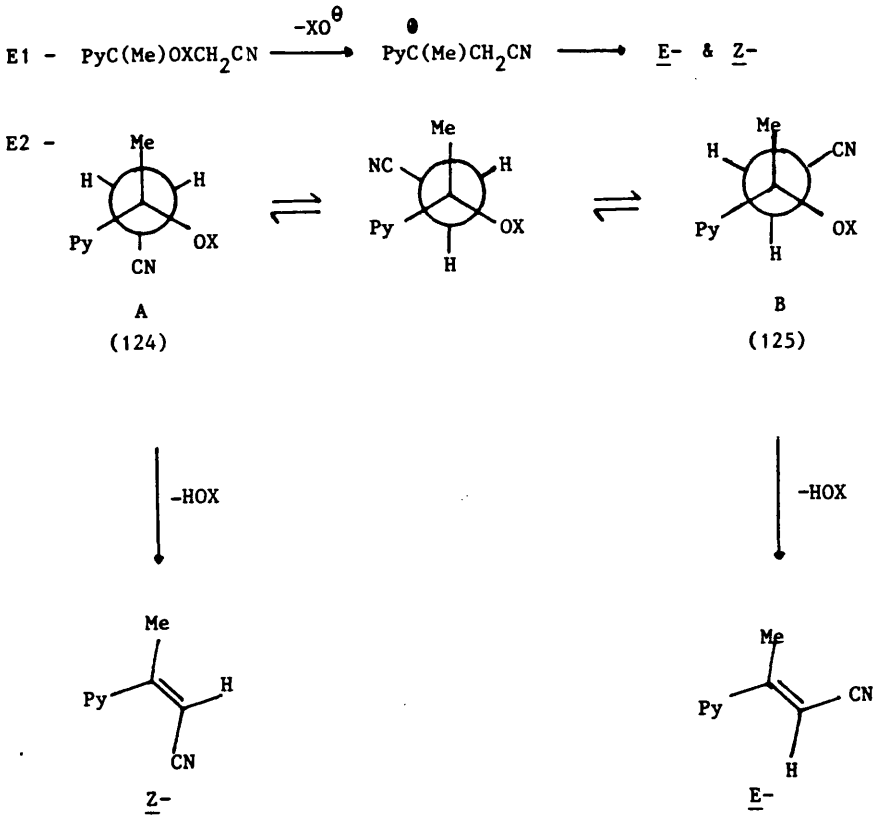
E-



Z-

We assume that the lower field position for the methyl resonances in our isomers compared to the crotonyl compounds is simply due to the deshielding influence of the 3-pyridyl substituent. Interestingly the most abundant isomer is the more thermodynamically stable from a geometric standpoint (methyl versus cyano as compared with pyridyl versus cyano) and also because it has the lower dipole moment. Since the alcohol in this case is tertiary and benzylic one might

suppose that an E1 mechanism occurs here affording the more stable alkene. However in an E2 process two conformational arrangements of an O-phosphorylated intermediate provide the necessary trans antiperiplanar geometries for a conserted elimination, and when one considers these it appears that the conformer A (124) is energetically somewhat less favoured than the conformer B (125), because of the greater non-bonded interaction within it. An E2 reaction from the favoured conformer affords the E-alkene which is also in line with our observations (Scheme 13).



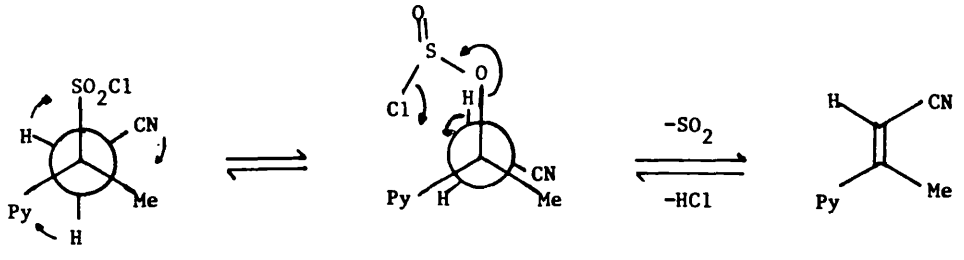
Py = 3-pyridyl; X = phosphorous bearing substituent.

Scheme 13

Thus we are unable to decide unequivocally between the two mechanisms on the evidence so far but concurrently with this experiement a similar reaction was conducted using thionyl chloride

as reagent instead of phosphorus tribromide. Here the E- isomer was by far the predominant product 18:1. Should an E1 mechanism be followed in both phosphorus tribromide and thionyl chloride reactions the product ratio should remain the same. On the other hand, in an E2 process replacement of an O-phosphoryl (or even bromo) substituent by a chlorine atom should decrease the non-bonded interactions in the transition state corresponding to A (124) above and thus change the ratio of isomeric alkenes in favour (or more towards) the Z- form assuming, of course, that thionyl chloride converts the alcohol into the corresponding chloro derivative, perhaps by an S_Ni process.

One other suggestion for the thionyl chloride result concern an syn elimination from a sulphonyl ester which adopts a staggered conformation and involves the concerted loss of sulphur dioxide and hydrogen chloride (126). In such an arrangement the cyanide function preferably eclipses the methyl group rather than the pyridyl unit leading onto the E- isomer.



(126a) (126b) (122)

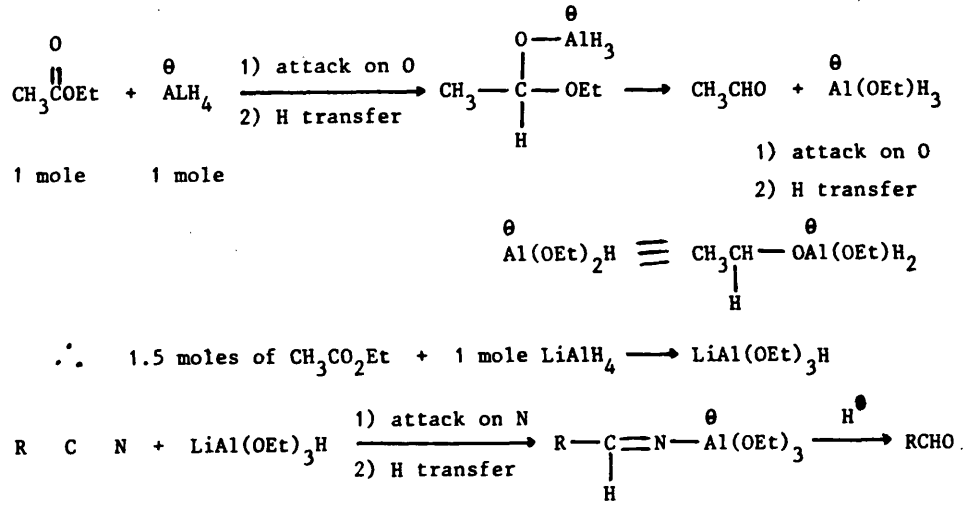
The whole set of arguments as they stand are rather specious and conclusions cannot be reached in the absence of kinetic evidence which may form a project for another research next year.

Sodium borohydride reduction of the mixed alkenes

afforded the saturated nitrile (116) in 94% yield as a single compound, which left only one more step to accomplish - the selective reduction of the nitrile to the aldehyde. Brown et al.,[89,90] have used lithiumalkoxyaluminium hydrides very successfully to reduce a variety of aliphatic and aromatic nitriles and at the time this reagent looked the most promising for our reduction since the similar reagent diisobutylaluminium hydride[91,92] was difficult to prepare and rather expensive to buy.

To a solution of lithiumaluminium hydride in dry diethyl-ether 1.5 molar equivalents of dry freshly distilled ethylacetate were added dropwise, maintaining the temperature at 0°C. Then the nitrile was added and the reaction mixture stirred for thirty minutes before work up for bases. A pale brown oil was thus obtained, thin layer chromatography of which indicated a mixture containing the starting material and new slower running component. In the infrared spectrum a cyanide absorption (ν_{max} 2224 cm^{-1}) and a carbonyl absorption (ν_{max} 1720 cm^{-1}) were observed. The P.M.R. spectrum confirmed that in addition to the starting material, a second compound namely an aldehyde (CHO at δ 9.60 ppm) was present and an inspection of the integration showed that the aldehyde was obtained in 30% yield.

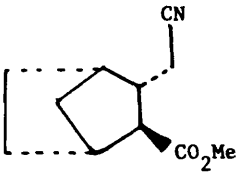
All attempts to optimise the conditions leading to this product were unsuccessful and the main reason for this failure seemed to be the problem of decomposition of lithiumaluminium hydride on storage. If the hydride content of the reagent is lower than the theoretical value, the reaction does not occur. The formation of the tri-alkoxyhydride is crucial for the success of the reduction and we were never quite sure that we were generating this species correctly.



Scheme 14

Next we attempted a Stephen's reduction of the unsaturated nitrile (115), which we hoped might function rather more like an arylcyanide since the double bond now conjugates the aryl nucleus with the nitrile function. Unfortunately this was not realised and little if any aldehyde was formed. From this result we turned to the reductions with the relatively expensive reagent diisobutylaluminium hydride.

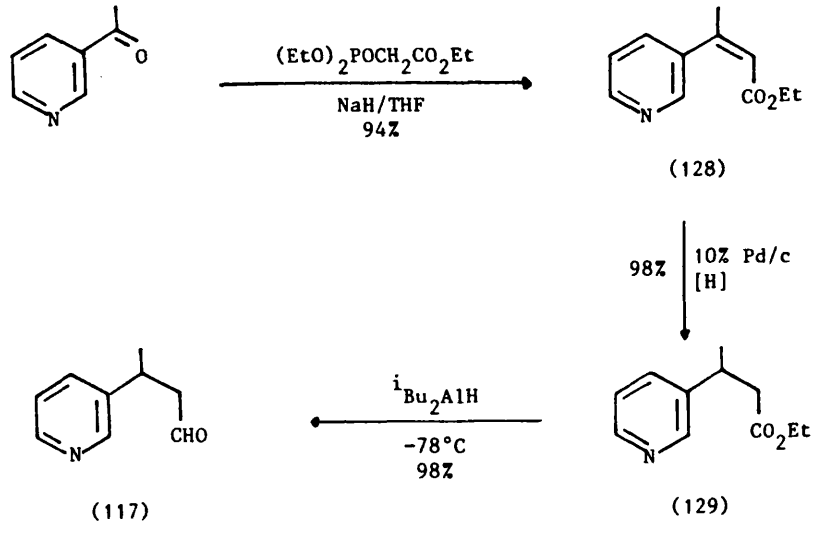
The nitrile (116) was added to a solution of the aluminium hydride in dry toluene at room temperature. On work up for bases the aldehyde was obtained in 40% yield. During our attempts to optimise the conditions of this reaction, we read with mixed feelings the fortunes of some Japanese chemists[93] who were attempting to synthesise protoglandin $H_2\alpha$. They needed to reduce the cyanide group in the intermediate (127) to the corresponding aldehyde. A ten molar excess of the reagent was needed to obtain a 26% yield of the aldehyde. During this reduction only a molar excess reduced the ester function to the aldehyde,[94] but left the cyanide intact. This made us feel that



(127)

in our work the compound to reduce was the corresponding ester rather than the nitrile.

Sugasawa and Matsuo[95] had already synthesised the α,β-unsaturated ester (128) in 80% yield by reacting ethoxycarbonylmethyltriphenylphosphonium bromide with 3-acetylpyridine. We preferred to use the more reactive and cheaper triethylphosphonoacetate,[78,96,97,98] and to a stirred suspension of sodium hydride in dry tetrahydrofuran, the phosphonoacetate was added dropwise and the reaction mixture stirred until the evolution of hydrogen had ceased. The 3-acetylpyridine was then added with stirring. Next day, work up for bases afforded the α,β-unsaturated ester (128) in 94% yield.



Scheme 15

It has been reported that the analogous 4-pyridylester on reduction with sodium borohydride[99] gave rise to a mixture of products which include the saturated ester (131) together with other products (see 130 → 133). Changing the molar ratio of the reagent was counterproductive. In view of this we chose to hydrogenate the α,β-unsaturated ester (128) over 10% palladium on carbon as catalyst. This reaction was very clean giving

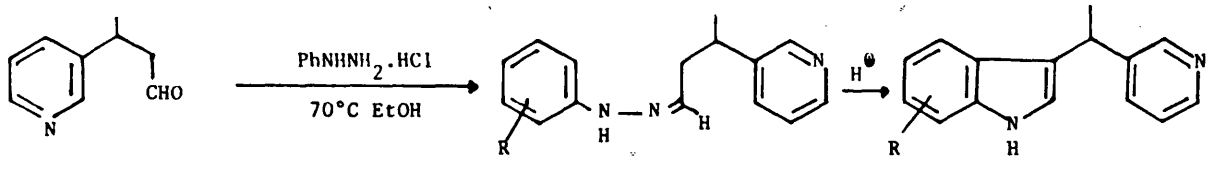
$$\underset{(130)}{\text{4-PyCH:CHCO}_2\text{Me}} \xrightarrow[\text{NaBH}_4,\ \Delta]{\text{MeOH}} \underset{(131)}{\text{4-Py(CH}_2)_2\text{CO}_2\text{Me}} + \underset{(132)}{\text{4-Py(CH}_2)_3\text{OH}} + \underset{(133)}{\text{4-PyCH:CHCH}_2\text{OH}}$$

1 mole — 2 moles — 34% — 8% — 22%

the saturated derivative (129) in 98% yield, and the final reduction to the aldehyde (117) was next attempted. Again we used diisobutylaluminium hydride as reagent and discovered that the best yield was obtained when 1.5 molar equivalents were employed in toluene maintained at -78°. The conversion was 93% efficient.

Synthesis of pyridylethyl indoles

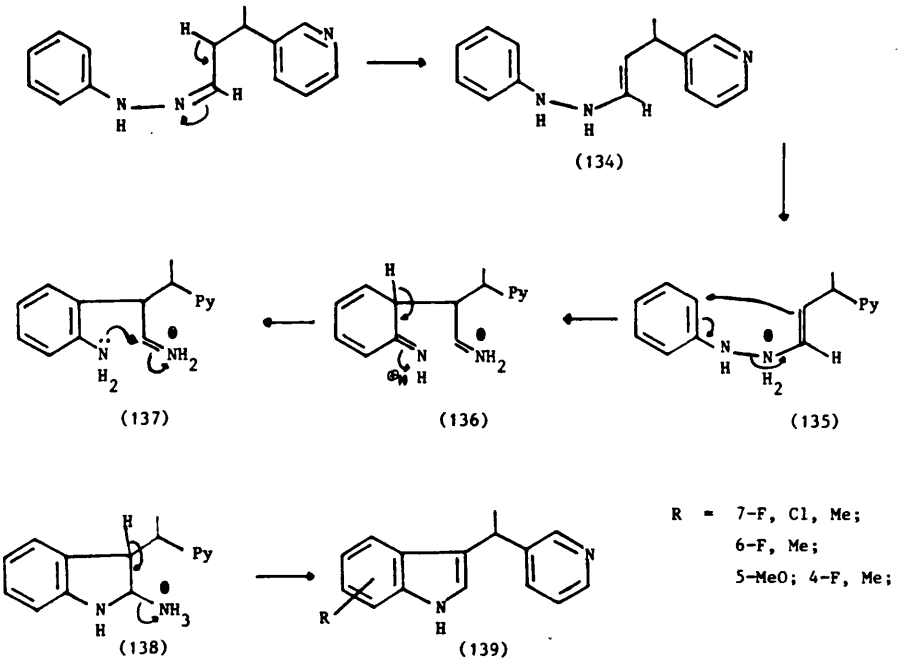
The next move in our projected synthesis was to form the appropriate hydrazones and attempt Fischer indole cyclisations



(53)

to pyridylethyl indoles (53). We executed this by first gently boiling the aldehyde and the arylhydrazines in ethanol solution (steam bath) to form the hydrazones which, without isolation, were treated with ethanolic hydrochloric acid.[100] The mixtures were then refluxed and the progress of the reactions monitored by TLC. For hydrazines bearing electron donating groups in the aryl nucleus, complete disappearence of the hydrazone derivative occurred within thirty minutes or so and on work up the corresponding pyridylethyl indoles (139) were obtained in 40-50% yield. As expected meta-substituted hydrazines lead to a mixture of 4- and 6-substituted products, the latter predominating. TLC analyses show that these can be separated, but time did not allow us to venture into this work which would have allowed access to the potentially interesting 10-substituted ellipticine series.

Moreover, further work on improving the indolisation procedure is obviously worthwhile and one might employ phosphoric acid rather than hydrogen chloride since the reagent is often deemed superior in the Fischer reaction.[101] Although we have no



Scheme 16

supporting evidence we assume that the mechanism of the indolisation reaction follows a conventional path and may thus be written down as shown in Scheme 16.

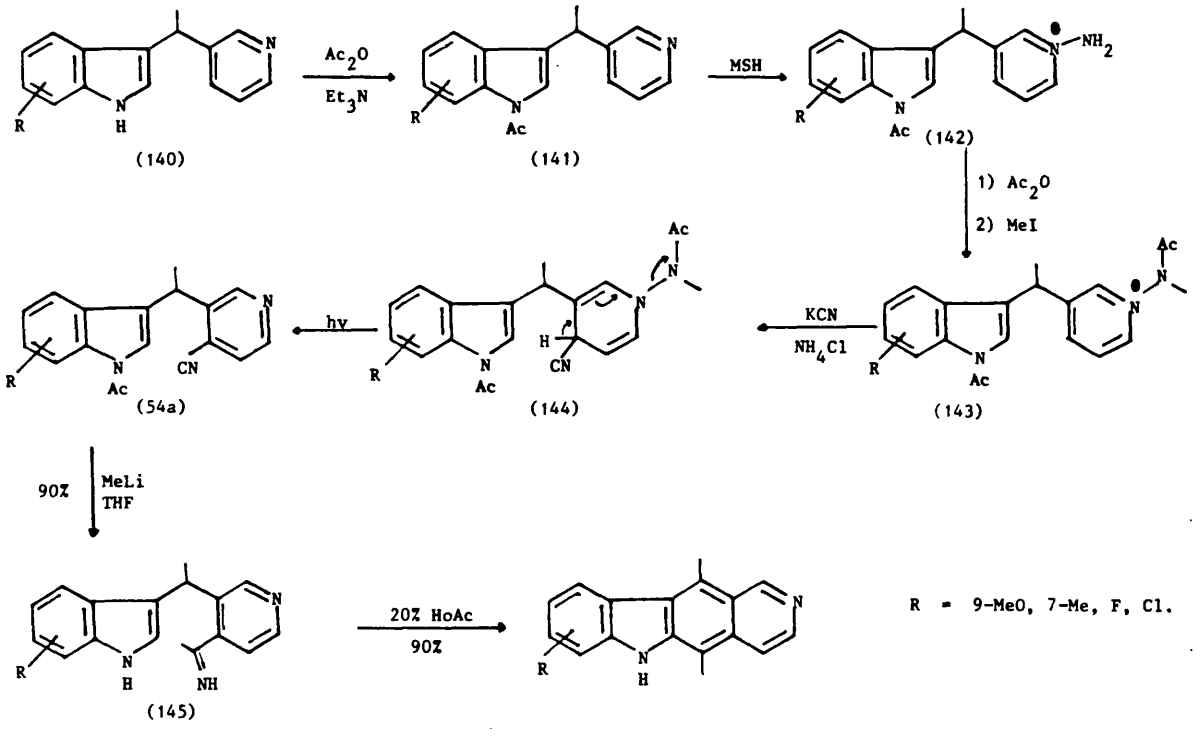
In order to test the viability of our synthesis we have prepared 7-chloro-, 7-fluoro-, 7-methyl- and 5-methoxy- (number refers to position in the indole nucleus) derivatives of the pyridylethyl indoles in the pure state and carried them forward to the corresponding ellipticines.

The choice of these derivatives was not entirely arbitrary, 9-methoxyellipticine is a known compound and its synthesis thus allows us to verify the authenticity of our precursors and, moreover, that the final step in our overall synthesis of pyrido[4,3-b]carbazoles is regiospecific. Ellipticines with a

substituent in the 7-position are obvious targets from a pharmacological point of view since they should inhibit "wasteful" hydroxylation at this site during the assumed enzymatic activation of the tetracyclic system.

Synthesis of ellipticines

The pyridylethyl indoles (140) were separately heated at reflux in acetic anhydride and triethylamine to yield the acetylated indoles (141). N-Amination of the pyridine molecule,



Scheme 17

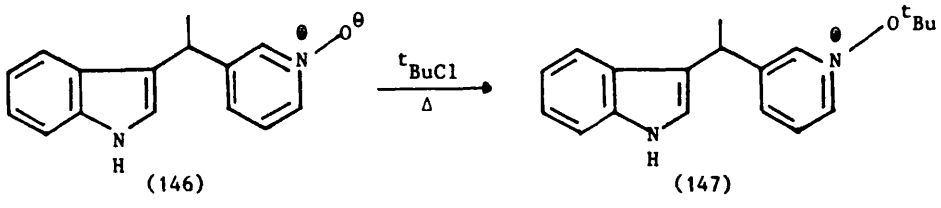
followed by acetylation and methylation afforded the methiodides (143). These methiodides were dissolved in water and treated with a potassium cyanide solution buffered with ammonium chloride to give the dihydropyridine (144) which on irradiation with soft u.v. light gave the nitriles (54a). The nitriles were then treated with four molar excess of methyllithium in tetrahydrofuran and on work up this gave the imines (145) which on treatment with hot 20% aqueous acetic acid afforded

the appropriate ellipticines in ~90% yield overall.

Thus we eventually formulated a novel versatile synthesis of ellipticine and its derivatives which did not depend on presynthesising the indole moiety. The overall yield of the sequence is approximately 20% and there is still room for improvement.

One relatively clumsy feature is the necessity to generate in steps a relatively large activating group on the pyridine nucleus prior to introduction of the cyanide function. It is not so much the case that the amination step itself and the subsequent acylation and alkylation of the N-amino group are unproductive, it is the difficulty in generating the aminating reagent hydroxylamine-O-mesitylenesulphonate.

Work here is still in progress to overcome this problem and one approach is to utilise pyridine N-oxide[102] derivatives such as the structure (147) which still retains the bulk necessary to direct a regioselective entry of the cyanide ion into the γ- rather than α-position(s) of the salt.

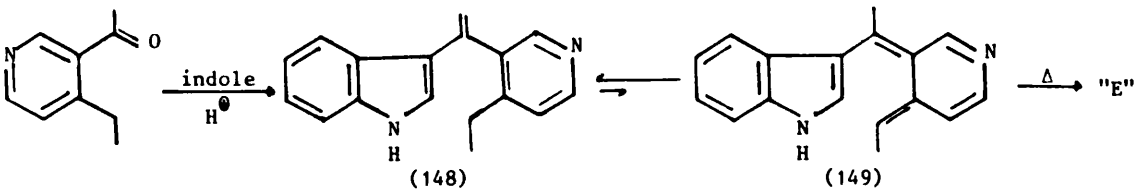


(146) (147)

Synthesis of 3-[3'-(6'-ethylpyridyl)ethyl]indole.

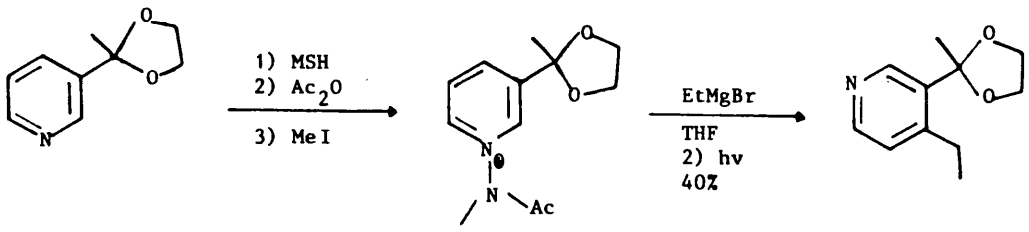
In Bergman and Carlson's work towards a synthesis of ellipticine (see Route 2, p. 13) they noted that when the indole moiety bore an ethyl group at position 2 condensation with 3-acetylpyridine gave a 1:1 reaction product (6). They assumed that further reaction on to the 2:1 product is inhibited by steric factors.

If this is so then a similar reaction between indole and 3-acetyl-4-ethylpyridine should give the pyridylindolyl derivative (148) which on heating might tautomerise to some extent and thus permit an electrocyclisation to the ellipticine



(148) (149)

system. Thus in the remainder of our time at Bath we attempted the synthesis of the required pyridine (152). The route attempted is an obvious extension of that used to make 3-acetyl-4-cyanopyridine by Webb, except a Grignard reagent now replaces cyanide ion as the nucleophile in the final step.

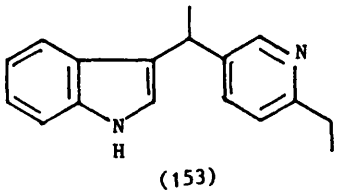


(150) (151) (152)

Addition of ethylmagnesiumbromide to the salt (151) afforded the acetal derivative of an acetylethylpyridine which was reacted with indole in ethanolichydrogen chloride to give a pink coloured solid, the PMR spectrum of which showed two peaks at δ 10.8 and δ 11.37 ppm, both exchanged by deuterium. Attempts to crystallise this product were unsuccessful and a TLC analyses in a variety of solvents only produced streaks rather than well defined spots.

Thinking that perhaps this material contained some of the

required product, a conclusion seemingly verified by a molecular ion peak at m/e 248 (expected for structure 148), we attempted to purify it by sublimation and to our surprise obtained a pure sample of a pyridylethyl indole which from the PMR spectrym was clearly a 3,6-disubstituted pyridine (153) rather than a 3,4-derivative.

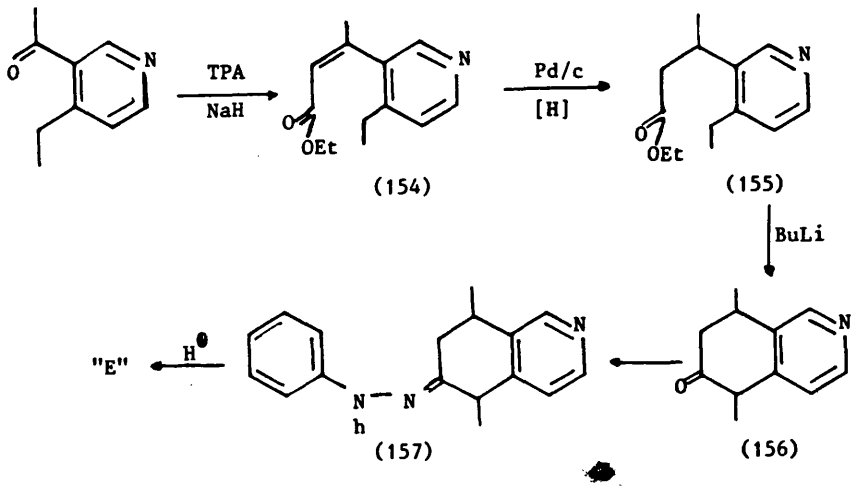


(153)

It is well known that the α-protons of pyridines resonate at δ 8.55-8.35 ppm, but in the spectrum of this product only one low field resonance at δ 8.45 ppm was noted although the signals for the protons of the ring form an AMX pattern.

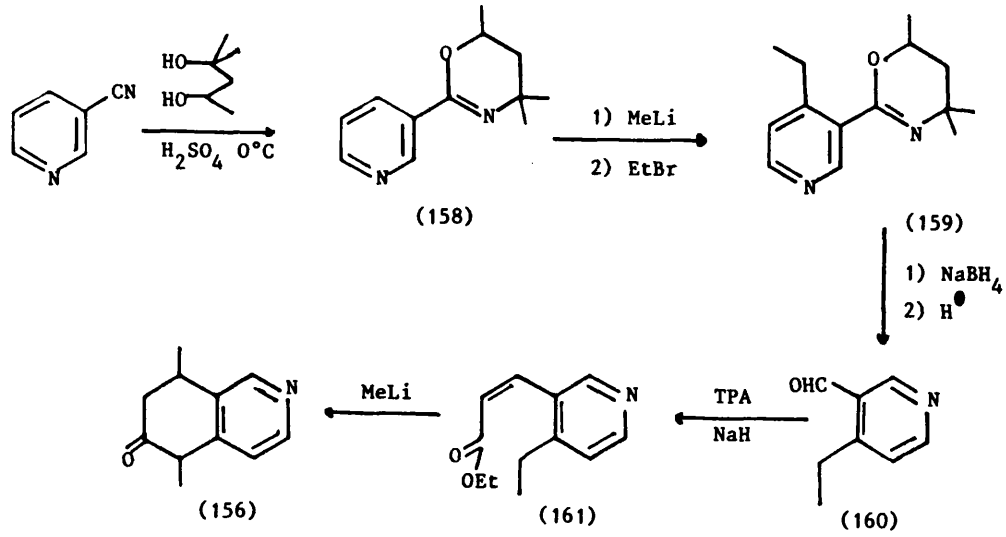
Obviously attack of the Grignard reagent occurs in the salt (151) at C-6^1 rather than at C-4^1 presumably for steric reasons, and the fact that this point was overlooked at the time is partly excused by our erroneous assumption that the C-2^1 proton resonance in the spectrum of the acetal (152) was shielded by the adjacent acetal function forced into an appropriate conformation by the neighbouring ethyl function.

The formation of the pyridylethyl indole (153) rather than the corresponding ethene of (148) is very interesting because a reductive step somewhere en route to it is required. The yield of this compound is such that it is a major component in the mixture but certainly not the only one. Thus it will be instructive to re-examine this reaction in order to deduce the nature of the remaining products and work is already in progress to complete this study. Should 3-acetyl-4-ethylpyridine become readily available the construction of the tetrahydroisoquinolone (156) might be achieved as illustrated in Scheme 18.



Scheme 18

Such a compound should afford dihydroellipticines directly through indolisation by the Fischer technique. Disappointed that we could not immediately adapt Webb's synthesis to our needs we now considered an alternative route based upon the work of Giam and Hauck,[103] and Meyers and Gabel[104] who have shown that it is possible to alkylate 3-(2-oxazolyl) pyridine with lithium alkyls. We considered the following sequence (Scheme 19), speculating that the six membered oxazine



Scheme 19

ring in (158) should add more stabilisation than the five membered oxazolines. Thus we synthesised the oxazine (158) in good yield following the usual oxazine synthesis.[105]

At the time of the preparation of this thesis the feasibility of this reaction has not yet been realised.

EXPERIMENTAL

EXPERIMENTAL

Instrumentation

All melting points were recorded on a Gallenkamf apparatus and are uncorrected. Ultra-violet spectra were recorded for 95% ethanolic solutions on a Perkin-Elmer 402 and 550-S ultra-violet and visible spectrophotometers. Intra-red spectra were run as Nujol mulls, potassium bromide discs or as liquid films (as specified N, P or L respectively) on a Perkin-Elmer 197 instrument. Proton magnetic resonance spectra were recorded on a J.E.O.L. PS100 instrument at 100 MHz and ^{13}carbon magnetic resonance spectra were recorded on a J.E.O.L. FX90Q instrument at 22.5 MHz. Chemical shifts are expressed in parts per million downfield from tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on an A.E.I. MS12 instrument at 12 and 70 eV.

Reagents

Commercial sodium hydride 50% oil dispersion was used. Tetrahydrofuran was distilled over lithium aluminium hydride and all other solvents used were dried and distilled following the procedure outlined in Vogel's practical book.

Unless otherwise stated all organic solutions were dried over anhydrous magnesium sulphate and the solvents evaporated *in vacuo*.

1-Ethoxy-1-oximidoethane

Hydrogen chloride was bubbled into a cooled, stirred solution of dry acetonitrile (105g, 1 mol.eq.), absolute ethanol (119g, 1 mol.eq.), diethylether (150 cm^3) during the course of eight hours.

The solution was reduced in volume by ~80% and the ensuing white slurry was poured cautiously onto crushed ice (700 g) containing potassium carbonate (225 g, 2 mol.eq.). The basic mixutre was shaken vigorously for ten minutes and then extracted with ether (5 x 150 cm^3).

The combined ether extracts were washed with water (3 x 50 cm^3) and treated with a cool (0°) solution of hydroxylamine hydrochloride (60 g, 1.2 mol.eq.) in water 250 cm^3) and shaken vigorously for twenty minutes.

The aqueous layer separated and was further extracted with ether (3 x 100 cm^3), dried and evaporated to give a vicous oil.

I.R. (L) ν_{max} cm^{-1}, 3600-3200 (OH), 1665 (C=N).

P.M.R. $\delta(CDCl_3)$ ppm, 8.50 (1H, brs, O$\underline{H}$), 3.90 (2H, q, C$\underline{H}_2$CH$_3$), 1.86 (3H, s, C$\underline{H}_3$-C), 1.15 (3H, t, C$\underline{H}_3$-CH$_2$).

Mesitylenesulphonyl chloride (MSC)

To cooled, well stirred chlorosulphonic acid (165 cm^3), mesitylene (85 cm^3) was added dropwise keeping the temperature below 5°. The resulting amber solution was further stirred in the cold for an hour, then poured onto crushed ice (1 Kg), whereupon a white solid formed. This was collected, well washed with 50% sodium carbonate solution, then water and air dried (150 g, 94%).

m.p. 50-2° (lit.,[59] 51-52°).

P.M.R. $\delta(CDCl_3)$ ppm, 7.16 (2H, s, H-3,5), 2.73 (6H, s, 2 x C$\underline{H}_3$), 2.72 (3H, s, C$\underline{H}_3$).

Ethyl O-mesitylenesulphonylacetohydroxamate

Mesitylenesulphonyl chloride (85 g) was added portionwise to a cooled (15°), well stirred solution of the oximidoethane (40 g)

in dimethylformamide (150 cm^3) and triethylamine (44 g). The resulting amber solution was stirred for a further hour at room temperature before being poured onto crushed ice and well agitated. A beige solid formed, which was collected and stored in the freezer (95 g, 85%).

I.R. (N) ν_{max} cm^{-1}, 1645 (C=N), 1360, 1180 (SO_2O).

O-Mesitylenesulphonylhydroxylamine (MSH)

To the hydroxamate (40 g), 70% perchloric acid (104 cm^3) was added and the mixture stirred until solution was effected. This was poured onto crushed ice (500 g) whereupon a white solid formed. This was collected, washed with 10% sodium bicarbonate solution (3 x 75 cm^3) and then with water (3 x 75 cm^3), air dried for a short time and used immediately (20 g, 68%).

I.R. (N) ν_{max} cm^{-1}, 3270, 3230 (NH_2), 1360, 1170 (SO_2O).

3-(1-Hydroxyethyl)pyridine (56)

Sodium borohydride (20 g) was added portionwise to a cooled well stirred solution of 3-acetylpyridine (50 g) in 95% ethanol (250 cm^3). The resulting pale yellow solution was diluted with water (250 cm^3) and left to stir.

Next morning it was extracted with dichloromethane (5 x 150 cm^3), dried and evaporated to give a pale yellow oil (49 g, 97%).

U.V. λ_{max} (ε) n.m., 263 (6, 520), 256 (5, 830), 268 (4, 690).

I.R. (L) ν_{max} cm^{-1}, 3,500-3,100 (OH), 1590 (py).

P.M.R. $\delta(CDCl_3)$ ppm, 8.4 (1H, d, $\underline{J}=2H_z$, H-2), 8.3, 8.25 (1H, dd, $\underline{J}=2H_z$, $\underline{J}=6H_z$, H-6), 7.74 (1H, m, H-4), 7.25 (1H, dd, $\underline{J}_1=\underline{J}_2=6H_z$, H-5), 6.15 (1H, brs, O-$\underline{H}$), 4.85 (1H, q, $\underline{J}=8H_z$, $C\underline{H}-CH_3$), 1.46 (3H, d, $\underline{J}=8H_z$, $C\underline{H}_3-CH$).

3-(1-Chloroethyl)pyridine (57)

Freshly distilled thionyl chloride (75 cm^3) was added dropwise to a cooled (0-5°) and mechanically stirred solution of the pyridine alcohol (10 g) in dry benzene (50 cm^3) maintaining the temperature at 0-5°. The reaction mixture was then stirred for a further hour in the cold. The resulting pale yellow solution was evaporated to dryness to yield a white solid, which was dissolved in ice water (100 cm^3), basified and extracted with ether (5 x 100 cm^3), dried and evaporated to give a light yellow oil (11 g, 94%).

P.M.R. $\delta(CDCl_3)$ ppm, 8.61 (1H, d, $\underline{J}=2H_z$, H-2), 8.5, 8.45 (1H, dd, $\underline{J}=2H_z$, $\underline{J}=6H_z$, H-6), 7.7 (1H, m, H-4), 7.24, 7.16 (1H, dd, $\underline{J}_1=\underline{J}_2=6H_z$, H-5), 5.08 (1H, q, $\underline{J}=8H_z$, $C\underline{H}-CH_3$), 1.8 (3H, d, $\underline{J}=8H_z$, $C\underline{H}_3-CH$).

3-(1-Methoxyethyl)pyridine (58)

The chloroethylpyridine (10 g) was added to a solution of sodium methoxide [sodium (5 g)] in dry methanol (75 cm^3) and the mixture heated at reflux for 5 hours. Excess solvent was then evaporated and the residue diluted with water (100 cm^3) and extracted with ether (5 x 100 cm^3). The combined extracts were dried and evaporated to give an oil (7 g, 74%).

U.V. λ_{max} (ε) n.m., 255 (7, 370), 262 (7, 420), 268 (5, 790).

P.M.R. $\delta(CDCl_3)$ ppm, 8.6 (1H, d, $\underline{J}=2H_z$, H-2), 8.58, 8.52 (1H, dd, $\underline{J}=2H_z$, $\underline{J}=6H_z$, H-6), 7.7 (1H, m, H-4), 7.33, 7.24 (1H, dd, $\underline{J}_1=\underline{J}_2=6H_z$, H-5), 4.36 (1H, q, $\underline{J}=8H_z$, $C\underline{H}-CH_3$), 3.23 (3H, s, $C\underline{H}_3-O$), 1.45(3H, d, $\underline{J}=8H_z$, $C\underline{H}_3-CH$).

3-(1-Methoxyethyl)pyridine-4-carbonitrile (60)

A cold solution of MSH (47 g, 1 mol.eq.) in dichloromethane (130 cm^3) was added dropwise to an ice cold well stirred solution

of the pyridyl ether (30 g, 1 mol.eq.) in dichloromethane (90 cm^3) and stirred for an additional thirty minutes at room temperature.

The orangish solution was poured into dry ether (1 l) and cooled, whereupon a yellow oil settled. The ether was decanted and the oil was dissolved in ice water (250 cm^3), treated with acetic anhydride (75 cm^3) and stirred in the cold for fifteen minutes. The resulting solution was basified and extracted with dichloromethane (5 x 100 cm^3), dried and evaporated. In this way an oil was obtained which was dissolved in acetone (25 cm^3) containing iodomethane (100 cm^3) and heated under reflux for forty-five minutes. The excess solvent was evaporated and the resulting oil (2.5 g) was dissolved in a warm solution of ammonium chloride (0.6 g) in water (30 cm^3), and treated with a solution of potassium cyanide (0.6 g) in water (20 cm^3). The reaction mixture was stirred at room temperature for a further hour, after which time a brown oil had separated out. The solution was extracted with dichloromethane (5 x 50 cm^3), washed with water (3 x 25 cm^3), dried and evaporated to give an amber oil which was dissolved in 95% ethanol (50 cm^3) and irradiated with soft U.V. light for thirty minutes. The solvent was then removed and the residue chromatographed on basic alumina eluting with ether to afford the title compound as a colourless oil.[59]

U.V. $\lambda_{max}(\varepsilon)$ n.m., 282 (13,400).

I.R.(L) ν_{max} cm^{-1}, 2210 (CN).

P.M.R. $\delta(CDCl_3)$ ppm, 8.9 (1H, s, H-2), 8.7 (1H, d, $\underline{J}=6H_z$, H-6), 7.85 (1H, d, $\underline{J}=6H_z$, H-5), 4.5 (1H, q, $\underline{J}=8H_z$, $C\underline{H}-CH_3$), 3.35 (3H, s, $C\underline{H}_3-O$), 1.3 (3H, d, $\underline{J}=8H_z$, $C\underline{H}_3$).

4-Acetyl-3-(1-methoxyethyl)pyridine (10)

The pyridine nitrile (2.5 g, 1 mol.eq.) in dry ether (50 cm^3) was added dropwise to a stirred, cooled solution of methyl lithium (2M, 9.7 cm^3, 1.2 mol.eq.) in dry ether and stirred for a further thirty minutes in the cold.

Then an ice cold solution of ammonium chloride (2 g) in water (10 cm^3) was added slowly, follwed by ice cold 1% sodium carbonate solution (100 cm^3). The mixture was extracted with dichloromethane (5 x 75 cm^3), dried and evaporated to give a colourless oil (2.4 g).

I.R.(L) ν_{max} cm^{-1}, 3230 (NH), 1650 (C=N).

This oil was stirred in 20% aqueous acetic acid (50 cm^3) for thirty minutes, basified and extracted with dichloromethane (3 x 100 cm^3) The combined extracts were dried and evaporated to give an amber oil (2.5 g, 88%).

U.V. λ_{max} (ε) n.m., 249 (12,500).

I.R.(L) ν_{max} cm^{-1}, 1700 (CO).

P.M.R. $\delta(CDCl_3)$ ppm, 8.90 (1H, s, H-2), 8.70 (1H, d, $\underline{J}=6H_z$, H-6), 7.85 (1H, d, $\underline{J}=6H_z$, H-5), 4.40 (1H, q, $\underline{J}=8H_z$, $C\underline{H}-CH_3$), 3.35 (3H, s, $C\underline{H}_3-O$), 2.60 (3H, s, $C\underline{H}_3CO$), 1.35 (3H, d, $\underline{J}=8H_z$, $C\underline{H}_3-CH$).

5-Acetamido-2-{1-[3-methoxyethyl)-4-pyridyl]ethylidene}indolin-3-one (61)

To a stirred solution of the acetylpyridine (2.5 g, 1 mol.eq.) in deoxygenated dry methanol (25 cm^3), under nitrogen, was added 5-acetamido-1-acetylindol-3-yl acetate (4.1 g, 1.1 mol.eq.), followed by a solution of potassium hydroxide (12.4 g) in deoxygenated water (25 cm^3). An immediate red colouration developed and the reaction vessel was then sealed up and left at room

temperature for a week. After this time the deep red viscous reaction mixture was poured slowly onto crushed ice (400 g) containing acetic acid (25 cm^3). The resulting basic solution was extracted with dichloromethane (5 x 150 cm^3), dried and evaporated to give a deep red solid (3.7 g, 70%).

U.V. λ_{max} (ϵ) n.m., 269 (22,100), 290 (14,500).

5-Acetamido-2-{1-[3(1-methoxyethyl)-4-pyridyl]ethyl}indole (11a)

The red solid from the previous experiment (1 g) was dissolved in 95% ethanol (100 cm^3) and heated at reflux under nitrogen for an hour, and sodium borohydride (5 g) was added in small portions. The excess solvent was then evaporated and the slurry was poured into ice cold water (100 cm^3) and extracted with dichloromethane (5 x 100 cm^3), dried and evaporated.

The ensuing green gum was dissolved in methanol and saturated with hydrogen chloride. The solvent was removed and the red residue dissolved in ice water (100 cm^3), basified and extracted with dichloromethane (5 x 100 cm^3). On evaporation of the combined extracts a viscous oil was obtained but all attempts to crystallise this product were unfruitful.

U.V. λ_{max} (ϵ) n.m., 243 (31,000), 301 (9,150), 311 (8,400).

9-Aminoellipticine

The viscous oil from the previous experiment was dissolved in 60% aqueous hydrobromic acid and heated at reflux for 10 hours. The yellow solid was collected, dissolved in water, basified, and extracted with ethylacetate (3 x 100 cm^3). On evaporation a faint brown solid (12 mg) was obtained. m.p. 255-260°dec., (lit.,[59] 258°dec.).

M.S. m/e (int %)., 261 (100), 246 (45), 231 (9), 219 (5), 151 (10).

U.V. λ_{max} (ε) n.m., 253 (12,600), 283 (36,800), 297 (42,500), 341 (6,370), 358 (4,150), 420 (3,240).

I.R.(N) ν_{max} cm^{-1}, 3130 (NH), 1620 (Ar), 1595 (py).

P.M.R. $\delta(CDCl_3)$ ppm, 10.8 (1H, s, NH), 9.6 (1H, s, H-1), 8.35 (1H, d, J=6H_z, H-3), 7.8 (1H, d, J=6H_z, H-4), 7.65 (1H, s, H-10), 7.3 (1H, d, J=8H_z, H-7), 6.9 (1H, d, J=8H_z, H-8), 4.8 (2H, brs, NH_2), 3.2 (3H, s, 11-CH_3), 2.7 (3H, s, 5-CH_3).

Ethyl 2-methylacetoacetate

Ethylacetoacetate (130 g, 1 mol.eq.) was added to a cooled solution of sodium ethoxide [sodium (23 g)] in absolute ethanol (400 cm^3) and the mixture heated at reflux for 3 hours to give a yellow solution.

This was cooled, and iodomethane (280 g, 2 mol.eq.) added with vigorous stirring. An exothermic reaction occured, after which the reactants were boiled for a further 3 hours and then allowed to cool overnight.

The product was added to ice water (750 cm^3) and extracted with dichloromethane (10 x 200 cm^3). The combined extracts were dried and evaporated to give a sweet smelling yellow oil (140 g, 98%).

P.M.R. $\delta(CDCl_3)$ ppm, 4.15 (2H, q, J=8H_z, CH_2CH_3), 3.52 (1H, q, J=6H_z, CH-CH_3), 2.21 (3H, s, CH_3-CO), 1.7-1.24 (6H, m, CH_3-CH, CH_3-CH_2).

Ethyl 5-methoxyindole-2-carboxylate (65)

Sodium nitrite (2.46 g, 1.1 mol.eq.) in water (10 cm^3) was added dropwise to a cooled (0-5°), stirred solution of 4-anisidine (4 g, 1 mol.eq.) in concentrated hydrochloric acid (20 cm^3). The reactants were stirred for a further ten minutes before the excess

acid was neutralised by the cautious addition of sodium acetate.

Simultaneously a cooled solution of potassium hydroxide (2 g, 1.1 mol.eq.) in water (5 cm^3) was added dropwise to a cooled (0°), stirred solution of ethyl 2-methylacetoacetate (5.2 g, 1.1 mol.eq.) in absolute ethanol (25 cm^3), followed immediately by the further addition of crushed ice (75 g).

To this mixture the diazotised anisidine was added in a stream with vigorous stirring, a yellow colouration developed that abruptly turned red. The resulting solution was brought to pH 6.5 by the addition of a few drops of concentrated hydrochloric acid and then left to stand overnight in the ice box (0°).

Then the whole was extracted with dichloromethane (5 x 75 cm^3), dried and evaporated to give a red oil (10.8 g, 100%).

I.R.(L) ν_{max} cm^{-1}, 3300, 3200 (NH), 1710 (CO).

Next this oil was added dropwise into pre-warmed (65°) 3N ethanolic hydrochloric acid (250 cm^3). An exothermic reaction occurred giving a dark solution which was boiled for a further twenty minutes before being poured into a beaker and left to evaporate to low bulk during the course of the night.

By next morning a solid had formed, which was collected at the pump and washed with water to give a pale greenish yellow solid (5.3 g, 73%).

m.p. 150° (lit.,[49] 152°).

U.V. λ_{max} n.m., 220, 300.

I.R.(P) ν_{max} cm^{-1}, 3400 (NH), 1730 (CO).

P.M.R. $\delta(CDCl_3)$ ppm, 9.02 (1H, brs, NH), 7.35 (1H, d, $J=8H_z$, H-7), 7.16 (1H, s, H-3), 7.08 (1H, d, $J=2H_z$, H-4), 7.04, 6.96 (1H, dd,

$\underline{J}=2H_z$, $\underline{J}=8H_z$, H-6), 4.41 (2H, q, $\underline{J}=8H_z$, $C\underline{H}_2CH_3$), 3.85 (3H, s, $C\underline{H}_3$-O), 1.41 (3H, t, $\underline{J}=8H_z$, $C\underline{H}_3$-CH_2).

5-Methoxyindole-2-carboxylic acid (66)

The ester (2 g, 1 mol.eq.) from the previous experiment and potassium hydroxide (1.53 g, 3 mol.eq.) were heated at reflux for two hours in water (20 cm^3). The clear orange solution thus formed was poured into ice water (20 cm^3) and acidified in the cold. The white solid that formed was then collected (1.6 g, 91%).

m.p. 200° (lit.,[49] 201°).

P.M.R. $\delta(d^6DMSO)$ ppm, 10.92 (1H, brs, COO$\underline{H}$), 8.92 (1H, brs, N$\underline{H}$), 7.38 (1H, d, $\underline{J}=8H_z$, H-7), 7.08 (1H, s, H-3), 7.02 (1H, d, $\underline{J}=2H_z$, H-4), 6.92, 6.84 (1H, dd, $\underline{J}=2H_z$, $\underline{J}=8H_z$, H-6), 3.79 (3H, s, $C\underline{H}_3$-O).

5-Methoxyindole (68)

The ammonium salt (5 g) and glycerol (10 cm^3) were stirred at 200-210° (internal temperature) under nitrogen for an hour. Then the dark brown melt was poured into ice water (300 cm^3) containing sodium carbonate (15 g). Immediately a gum was formed, which was dissolved in dichloromethane (500 cm^3) and washed with saturated sodium carbonate (3 x 25 cm^3) and then with water (3 x 25 cm^3). The combined solvent layers were then dried and evaporated to give a viscous brown oil, which solidified on standing in the fridge (3.34 g, 94%).

m.p. 55° (lit.,[49] 56°).

I.R.(P) ν_{max} cm^{-1}, 3510, 3410 (NH).

P.M.R. $\delta(CDCl_3)$ ppm, 8.05 (1H, brs, NH), 7.05 (1H, d, $\underline{J}=8H_z$, H-7), 7.00 (1H, s, H-3), 6.92 (1H, d, $\underline{J}=2H_z$, H-4), 6.79, 6.69 (1H, dd, $\underline{J}=2H_z$, $\underline{J}=8H_z$, H-6), 6.33 (1H, brs, H-2), 3.72 (3H, s, $C\underline{H}_3$-O).

3-[1-(3-Pyridyl)ethyl]-5-methoxyindole (69)

To dry magnesium turnings (1.3 g, 1.7 mol.eq.) in dry ether (250 cm^3), ethyl bromide (4.1 g, 1.1 mol.eq.) was added dropwise and the mixture stirred for a further hour, under nitrogen during which time a grey suspension formed.

To this cooled suspension, the indole (5 g, 1 mol.eq.) in dry ether (75 cm^3) was added dropwise over thirty minutes. An orange brown solid began to form almost immediately and this hindered the stirring. Therefore dry dichloromethane (5 cm^3) was added to obtain a more homogeneous reaction mixture. This was then allowed to warm to room temperature and stirred for a further hour.

Then the mixture was cooled to 0° and the chloropyridine (9.6 g, 2 mol.eq.) was added and the temperature allowed to warm to that of the laboratory. After stirring overnight under nitrogen the dark contents of the reaction flask were exaustingly extracted into 2M hydrochloric acid (20 x 50 cm^3), the acid solution washed with ether (3 x 100 cm^3) and then cooled before basification with ammonia. The basified solution was extracted with dichloromethane (5 x 200 cm^3) and the combined extracts dried and evaporated to give a reddish amber oil (10.3 g) which on trituration with ether gave the product as an off-white solid (0.55 g, 6%).

NOTES:

(1) The amber oil on column chromatography - basic alumina, ether eluant afforded pure chloroethylpyridine (6.2 g).

(2) The failure to add dichloromethane to facilitate the suspension of the indolylmagnesium bromide, resulted

in only a trace of product being isolated.

The use of tetrahydrofuran instead of dichloromethane gave a similar result.

(3) Keeping the reactants under nitrogen for different periods of time, (2 day → 2 weeks), did not increase the yield.

An improved experimental procedure

Ethylbromide (12.3 g, 1.1 mol.eq.) was added dropwise to stirred dry magnesium turnings (3.8 g, 1.6 mol.eq.) in dry tetrahydrofuran (150 cm^3) and the mixture left stirring for a further thirty minutes under nitrogen. To this grey solution the indole (15 g, 1 mol.eq.) in tetrahydrofuran (10 cm^3) was added dropwise over fifteen minutes. An immediate exothermic reaction occurred with effervesence. The whole was left stirring for a further hour before the chloropyridine (14.4 g, 1 mol.eq.) was added dropwise, again an exothermic reaction occurred. Next the reactants were sealed up and left aside for two days.

The whole reaction mixture was then evaporated to give a viscous slurry, which was worked up for bases as before to give a pale yellow oil, which on trituration (ether) afforded an off-white solid (7.9 g, 30%).

Chromatography on silica, using ether as eluant gave a white solid which re-crystallised from methanol as white needles.

m.p. 136-7°.

M.S. m/e (int %), M^+ 252 (63), 237 (100), 74 (21).

u.v. $\lambda_{max}(\varepsilon)$ n.m., 220 (25,940), 268 (7,660), 297 (5,360), 308 (3,890).

I.R.(P) ν_{max} cm^{-1}, 3180, 3160 (NH), 1620 (Ar), 1580, 1570 (py).

P.M.R. $\delta(d^6DMSO)$ ppm, 10.80 (1H, brs, NH), 8.61 (1H, d, $\underline{J}=2H_z$,

H-2'), 8.41, 8.36 (1H, dd, $\underline{J}$=2H_z, $\underline{J}$=6H_z, H-6'), 7.66 (1H, m, H-4'), 7.38-7.18 (3H, m, H-4,6&7), 6.83-6.65 (2H, m, H-5'&2), 4.36 (1H, q, $\underline{J}$=6H_z, C$\underline{H}$-CH_3), 3.66 (3H, s, C$\underline{H}_3$-O), 1.68 (3H, d, $\underline{J}$=6H_z, C$\underline{H}_3$-CH). [Found: C, 76.1; H, 6.31; N, 12.0 $C_{16}H_{16}N_2O$ requires: C, 76.19; H, 6.34; N, 11.11%].

2,4-Dinitrophenylacetonitrile (71)

Ethyl cyanoacetate (11.3 g, 1 mol.eq.) was added to a cooled, well stirred suspension of ground sodium hydroxide (4 g, 2 mol.eq.) in dry dimethylformamide (100 cm^3) followed by a solution of dinitrochlorobenzene (10.12 g, 1 mol.eq.) in dry dimethylformamide (10 cm^3). The whole was stirred at 20-25° for thirty minutes before the solvent was evaporated. The resulting dark red oil was dissolved in water (500 cm^3) and cautiously acidified and then extracted with ether (3 x 200 cm^3). The extracts were dried and evaporated to give a red oil (13.7 g, 98%). Next the red oil was stirred at 90° in 10% hydrochloric acid (200 cm^3) for four hours and cooled overnight. The next day the solution was extracted with ether (5 x 100 cm^3) and the combined extracts washed with sodium carbonate (2 x 50 cm^3), water (2 x 50 cm^3), dried and evaporated to give an oil, which solidified on standing. The product was re-crystallised from dichloromethane to give yellow needles (7.3 g, 68%).

m.p. 89° (lit.,[58] 89°).

u.v. λ_{max} n.m., 205, 240.

I.R.(P) ν_{max} cm^{-1}, 2250 (CN), 1520, 1340 (NO_2).

P.M.R. $\delta(CDCl_3)$ ppm, 8.9 (1H, d, $\underline{J}$=2H_z, H-3), 8.55, 8.45 (1H, dd, $\underline{J}$=2H_z, $\underline{J}$=8H_z, H-5), 7.95 (1H, d, $\underline{J}$=8H_z, H-6), 4.25 (2H, s, -C$\underline{H}_2$-CN).

Attempted condensations of 2,4-dinitrophenylacetonitrile with 3-acetylpyridine

Base catalysed reactions

(1) piperidine

Piperidine (0.5 cm^3) was added dropwise to a boiling solution of the nitrile (0.5 g, 1 mol.eq.), 3-acetylpyridine (0.3 g, 1 mol.eq.) in absolute ethanol (25 cm^3) under nitrogen. The solution thickened and turned dark green immediately. Next, the reaction mixture was boiled for thirty minutes, the vessel then sealed and left over the weekend at room temperature. The excess ethanol was then evaporated off to give a dark green oil.

On work up for bases an acid insoluble solid and acid soluble pale red oil were obtained. TLC on silica and alumina showed them to be unchanged nitrile and pyridine respectively. Confirmation was obtained by I.R. and P.M.R. spectroscopy.

(2) pyrrolidine

The nitrile (0.5 g, 1 mol.eq.), 3-acetylpyridine (0.3 g, 1 mol.eq.), and pyrrolidine (0.2 g) were heated under reflux in dry benzene (50 cm^3) using a Dean-Stark apparatus for six hours. The ensuing green solution was concentrated and left to stand. Since crystallisation did not occur it was worked up for bases as before. Again chromatographic and spectroscopic data showed that starting materials were present and that no product had formed.

(3) sodium hydroxide

The nitrile (2 g, 1 mol.eq.), powdered sodium hydroxide (0.5 g, 1 mol.eq.) in dry dimethylformamide (20 cm^3) were stirred under nitrogen for one hour before 3-acetylpyridine (2.4 g, 2 mol.eq.) was added and the temperature increased and maintained at 40° for

ten hours.

On work up for bases an intractable tar was obtained. Chromatographic analyses indicated it to be a multicomponent mixture.

Acid catalysed reactions

(4) ammonium acetate/acetic acid

3-Acetylpyridine (0.3 g, 1 mol.eq), the nitrile (0.5 g, 1 mol.eq.), glacial acetic acid (5 cm^3) and ammonium acetate (0.2 g) were boiled in dry benzene (50 cm^3) under Dean-Stark conditions over six hours.

On work up for bases an intractable gum was again obtained.

(5) ethanolic hydrochloric acid

Equimolar amounts of the pyridyl ketone and the nitrile (0.5 g) were heated at reflux in ethanolic hydrochloric acid for six hours.

On work up for bases unchanged 3-acetylpyridine was returned.

Attempted condensations of 2,4-dinitrophenylacetonitrile with 3-chloroethylpyridine

Base catalysed reactions

(1) sodium ethoxide

The nitrile (2 g, 1 mol.eq.) in absolute ethanol (5 cm^3) was added to a cooled stirred solution of sodium ethoxide [sodium (0.22 g, 1 mol.eq.)] in absolute ethanol (5 cm^3) under nitrogen, the resulting green solution was stirred for a further fifteen minutes before the addition of chloroethylpyridine (2 g, 1.5 mol.eq.).

An exothermic reaction occurred and the mixture was left over the weekend. On work up for bases this yielded a dark green gum. Chromatography on silica and then on alumina using different solvents gave streaks rather than well defined spots.

(2) lithium diisopropylamide

A solution of n-butyllithium (1.34 M, 1.8 cm^3, 1 mol.eq.) was added dropwise to a cooled (-78°) well stirred solution of diisopropylamine (0.25 g, 1 mol.eq.) in tetrahydrofuran (5 cm^3) under nitrogen. Next the nitrile (0.5 g, 1 mol.eq.) in tetrahydrofuran (5 cm^3) was added and the reaction mixture stirred for ten minutes, then the chloroethylpyridine (0.3 g, 1 mol.eq.) was introduced and the mixture allowed to warm to room temperature over one hour.

On work up for bases an intractable tar was obtained.

(3) lithium N-isopropylcyclohexylamide

The above experiment was repeated using N-isopropylcyclohexylamine but the result was the same.

Attempted condensations of 2,4-dinitrophenylacetonitrile with 3-pyridocarboaldehyde

Base catalysed reactions

(1) pyrrolidine

The nitrile (2 g, 1 mol.eq.), pyridine aldehyde (1.6 g, 1.5 mol.eq.) and pyrrolidine (0.5 g) were heated under reflux in dry benzene (25 cm^3) using a Dean-Stark apparatus for six hours.

On work up for bases starting material was returned.

(2) piperdine

Piperidine (1.5 cm^3) was added to a boiling solution of the nitrile (2 g, 1 mol.eq.), pyridine aldehyde (2.1g, 2 mol.eq.) in absolute ethanol (25 cm^3) under nitrogen. Then the contents of the vessel was heated at reflux for thirty minutes before being sealed up and left for a week at room temperature.

On work up for bases tarry products were obtained.

Acid catalysed reaction

(3) 4-toluenesulphonic acid

The nitrile (2 g, 1 mol.eq.), pyridine aldehyde (2.1 g, 2 mol.eq.) and 4-toluenesulphonic acid (4 g, 2.2 mol.eq.) were heated at reflux in dry benzene (50 cm^3) under Dean-Stark conditions for two days.

On work up for bases starting material was returned.

Ethyl 3-(3'-pyridyl)-2-cyanobut-2-enoate (75)

(1) sodium ethoxide

Ethyl cyanoacetate (7 g, 1.5 mol.eq.) was added dropwise to a mechanically stirred cold solution of sodium ethoxide [sodium (1.4 g, 1.5 mol.eq.)] in absolute ethanol (10 cm^3) under nitrogen. An exothermic reaction occurred resulting in a milky suspension that was stirred for an additional fifteen minutes before 3-acetyl-pyridine (5 g, 1 mol.eq.) was added dropwise. A cream solution was thus obtained, which when warmed gave a clear solution that rapidly changed colour to an orange gum. After a further hour the warm solution was added to ice water (100 cm^3) and then extracted with dichloromethane (5 x 50 cm^3). The combined extracts were dried and evaporated to give an oil (6 g).

Chromatographic analysis of this oil indicated that it contained only starting materials, a conclusion which was subsequently confirmed by spectroscopy.

(2) ammonium acetate/acetic acid (optimum conditions)

3-Acetylpyridine (10 g, 1 mol.eq.), ethylcyanoacetate (18.7 g, 2 mol.eq.) and glacial acetic acid (12.8 g, 2.6 mol.eq.) were boiled for two days in dry benzene (125 cm^3) using a Dean-Stark apparatus. To this ammonium acetate (8 g, 1.3 mol.eq.) was added portionwise at three hourly intervals.

The mixture was poured into ice water (300 cm^3), basified and extracted with ether (5 x 250 cm^3). The combined extracts were dried and evaporated to give an oil (30 g).

I.R.(L) ν_{max} cm^{-1}, 2260, 2225 (CN), 1750, 1720 (CO).

This oil was stirred with 35% sodium bisulphite solution (100 cm^3) overnight, diluted with water (200 cm^3) and washed with ether (3 x 100 cm^3). The aqueous phase was basified and extracted with ether (5 x 250 cm^3). The combined extracts were dried and evaporated to give a light yellow viscous oil (10.6 g).

I.R.(L) ν_{max} cm^{-1}, 2225 (CN), 1720, 1690 (CO).

On vacuum distillation, 3-acetylpyridine was collected at 79°/1 mmHg leaving the required unsaturated nitrile as a viscous brown oil (9.4 g, 52%).

U.V. λ_{max} n.m., 265.

I.R.(L) ν_{max} cm^{-1}, 2205 (CN), 1720 (CO).

P.M.R. $\delta(CDCl_3)$ ppm, 8.7 (2H, m, H-2'&6'), 7.8 (1H, m, H-4'), 7.4 (1H, m, H-5'), 4.3, 4.1 (2H, dq, $\underline{J}$=8H_z, $C\underline{H}_2CH_3$), 2.72, 2.57 (3H, ds, $C\underline{H}_3$-C=C), 1.4, 1.15 (3H, dt, $\underline{J}$=8H_z, $C\underline{H}_3$-CH_2).

Ethyl 3-(3'-pyridyl)-2-cyanobutanoate (76) (optimum conditions)

Sodium borohydride (0.18 g, 2 mol.eq.) was added all at once to a cooled (0°) stirred solution of the unsaturated nitrile (2 g, 1 mol.eq.) in isopropanol (25 cm^3) and the mixture stirred in the cold (0-5°) for another hour. It was next poured into ice water (100 cm^3), acidified and washed with ether (3 x 50 cm^3). The aqueous phase was separated, basified and extracted with ethyl acetate (5 x 75 cm^3). Finally the combined extracts were dried and evaporated to give an amber oil (1.8 g, 90%).

U.V. λ_{max} n.m., 260.

I.R. ν_{max} cm^{-1}, 2220 (CN), 1740 (CO).

P.M.R. $\delta(CDCl_3)$ ppm, 8.5 (2H, m, H-2'&6'), 7.7 (1H, m, H-4'), 7.35, 7.25 (1H, dd, $J_1=J_2=6H_z$, H-5'), 4.2 (2H, m, CH_2CH_3), 3.7 (2H, m, CH-CH-CH_3), 1.5 (3H, bd, $J=8H_z$, CH_3-CH), 1.2 (3H, m, CH_3-CH_2).

Attempted condensations of ethyl 3-(3'-pyridyl)-2-cyanobutanoate

Base catalysed reactions

(1) sodium hydroxide

A solution of the title ester (1.1 g, 2 mol.eq.) in dry dimethylformamide (5 cm^3) was added dropwise to a cooled, stirred suspension of ground sodium hydroxide (0.2 g, 2 mol.eq.) in dry dimethylformamide (15 cm^3). To the resulting pale amber solution, dinitrochlorobenzene (0.5 g, 1 mol.eq.) in dry dimethylformamide (5 cm^3) was added and stirred for an hour in the cold followed by a further two hours at room temperature. It was then evaporated to give a red residue. On work up for bases a red oil and a non-basic brownish solid was obtained.

Spectroscopic analysis confirmed initial chromatographic evidence that both fractions were multi-component mixtures.

(2) The above experiment was repeated using equimolar quantities of reactants and leaving the resultant mixture overnight at room temperature. On work up for bases the result was the same.

(3) The equimolar reaction was repeated, but the temperature increased to 60° for four hours before being sealed up for the weekend. This attempt also proved fruitless.

(4) sodium ethoxide

The ester (2 g, 1 mol.eq.) in absolute ethanol (5 cm^3) was added dropwise to a cooled stirred solution of sodium ethoxide

[sodium (0.2 g, 1 mol.eq.)] in absolute ethanol (5 cm^3) under a nitrogen atmosphere. The resulting pale orange solution was stirred at room temperature for fifteen minutes before 2,4-dinitrochlorobenzene (1.86 g, 1 mol.eq.) in absolute ethanol (5 cm^3) was added dropwise. The reaction mixture was then heated at reflux for three hours before being allowed to cool overnight. Next day a solid product which had formed was collected and identified as sodium chloride ($AgNO_3/NH_4OH$).

The filtrate was worked up for bases, to yield a viscous oil, chromatographic analysis of which showed it to be a multi-component mixture.

(5) lithium diisopropyl amide

Butyl lithium (1.5 M, 0.6 cm^3, 1 mol.eq.) was added dropwise to a cooled (-78°) stirred solution of diisopropylamine (0.09 g, 1 mol.eq.) in tetrahydrofuran (5 cm^3). To this the ester (0.2 g, 1 mol.eq.) in tetrahydrofuran (5 cm^3) was added and stirred for an hour before 2,4-dinitrochlorobenzene (0.19 g, 1 mol.eq.) in tetrahydrofuran (5 cm^3) was added dropwise and left stirring overnight at room temperature. The dark brown solution was worked up for bases and again showed a multiplet of spots on thin layer chromatographs.

(6) sodium hydride

The ester (2 g, 1 mol.eq.) in dry dimethylformamide (5 cm^3) was added dropwise to a cooled well stirred suspension of sodium hydride (0.44 g, 1 mol.eq.) in dry dimethylformamide (5 cm^3) under nitrogen. An exothermic reaction occurred with the evolution of a gas, but the temperature of the reactants were kept between -10°-0°. The reaction mixture was stirred at ~-5°

for a further thirty minutes and then for another thirty minutes at room temperature, after this time it was again cooled to ~-5° and the 2,4-dinitrochlorobenzene (1.9 g, 1 mol.eq.) in dimethylformamide (5 cm^3) added dropwise over thirty minutes maintaining the temperature at -10°. The reactants were allowed to warm to room temperature and maintained at these conditions for a day.

The resulting red solution was worked up for bases to give a red oil but again TLC analysis showed it to be a mixture of compounds.

Attempted condensation of 2-nitrophenylacetic acid

sodium amide

Finely cut sodium slices (2.5 g, 2 mol.eq.) were added portionwise to stirred liquified ammonia (500 cm^3) containing ferric nitrate (0.12 g) and to the resulting grey solution 2-nitrophenylacetic acid (9.9 g, 1 mol.eq.) was added and the mixture then stirred well for thirty minutes. To this red solution the chloroethylpyridine (7.7 g, 1 mol.eq.) in dry ether (15 cm^3) was added rapidly. Finally the reaction mixture was left stirring until all the ammonia had evaporated leaving a thick brown paste.

On work up for bases a near quantitative yield of the chloroethylpyridine (7.4 g) was obtained and also an acid insoluble solid (7.1 g), the TLC of which showed it to be a complex mixture.

Attempted condensation of ethyl 2-nitrophenylacetate

Base catalysed reactions

(1) piperidine

The nitrophenylacetate (2 g, 1 mol.eq.), 3-acetylpyridine (1.2 g, 1 mol.eq.) and piperidine (0.5 cm^3) were refluxed in dry benzene (50 cm^3) under Dean-Stark conditions for twenty hours.

On work up for bases unreacted 3-acetylpyridine was returned.

(2) pyrrolidine

The above experiment was repeated using pyrrolidine but with the same result.

(3) sodium ethoxide

A solution of the nitrophenylacetate (5 g, 1 mol.eq.) in absolute ethanol (10 cm^3) was added to a cooled solution of sodium ethoxide [sodium (0.55 g, 1 mol.eq.)] in absolute ethanol (5 cm^3) under nitrogen. Having stirred for thirty minutes the chloroethylpyridine (3.4 g, 1 mol.eq.) was added and the mixture boiled for five hours.

On work up for bases a multi-component mixture was obtained, also an acid insoluble solid (4.1 g) was identified as 2-nitrophenylacetic acid.

(4) lithium dicyclohexylamide

A solution of butyllithium (1.34 M, 17.8 cm^3, 1 mol.eq.) was added dropwise to a cooled (-78°) stirred solution of dicyclohexylamine (4.3 g, 1 mol.eq.) in tetrahydrofuran (25 cm^3) under an atmosphere of nitrogen. After a lapse of fifteen minutes the nitrophenylacetate (5 g, 1 mol.eq.) in tetrahydrofuran (25 cm^3) was added and the mixture well stirred for an hour. To the resulting blue solution, chloroethylpyridine (3.4 g, 1 mol.eq.) in tetrahydrofuran (10 cm^3) was added and the reaction mixture stirred in the cold for thirty minutes before it was allowed to warm to room temperature. Next day on work up for bases the chloropyridine and polymeric material were obtained.

Attempted condensation of ethyl 2-nitrophenylacetate with benzyl chloride

A solution of the nitrophenylacetate (2 g, 1 mol.eq.) in absolute ethanol (5 cm^3) was added dropwise to a cooled stirred solution of sodium ethoxide [sodium (0.2 g, 1 mol.eq)] in absolute ethanol (5 cm^3) under nitrogen and the mixture stirred for thirty minutes. Next benzyl chloride (1.2 g, 1 mol.eq.) was added and boiled for six hours.

On pouring the cooled mixture into ice cold dilute hydrochloric acid (100 cm^3) whereupon a cream coloured solid formed (1.8 g). This was re-crystallised from ethanol and shown to be 2-nitrophenylacetic acid.

2-Phenyl-3-(3'-pyridyl)butancarbonitrile (79)

Finely cut slices of potassium (2.8 g, 1 mol.eq.) were added portionwise to stirred liquified ammonia (500 cm^3) containing ferric nitrate (0.12 g). To the resulting grey solution phenylacetonitrile (8.3 g, 1 mol.eq.) was added dropwise and the ensuing green solution was stirred for a further fifteen minutes before the chloroethylpyridine (10 g, 1 mol.eq.) was added. The reaction mixture was then stirred until all the ammonia had evaporated to leave a white slurry. This was poured onto crushed ice and stirred, whereupon a gum formed which solidified on trituration with hot petrol

This product was re-crystallised from acetone as white needles (8.7 g, 54%).

m.p. 128-9°.

M.S. m/e (int. %) M^+ 222 (100), 106 (51).

U.V. λ_{max} n.m., 212, 257, 264, 271.

I.R.(P) ν_{max} cm^{-1}, 2250 (CN), 1590, 1575 (Py).

P.M.R. $\delta(d^6DMSO)$ ppm, 8.5 (2H, m, H-2'&6'), 7.78 (1H, m, H-4'), 7.4 (6H, m, H-5' & Ar-H), 4.58 (1H, d, $\underline{J}$=6H_z, NC-C$\underline{H}$-CH), 3.4 (1H, m, -CH-C$\underline{H}$-CH_3), 1.22 (3H, d, $\underline{J}$=8H_z, $C\underline{H}_3$-CH). [Found: C, 81.1; H, 6.3; N, 12.6 $C_{15}H_{14}N_2$ requires: C, 81.0; H, 6.4; N, 12.6%].

2-(4-Nitrophenyl)-3-(3'-pyridyl)butancarbonitrile (81) (optimum conditions)

The nitrile (3 g) was added in small portions to a cooled (0°) well stirred mixture of concentrated nitric acid (25 cm^3) and concentrated sulphuric acid (25 cm^3) and the mixture stirred in the cold for two hours. Next it was poured onto crushed ice, basified and extracted with ethylacetate (5 x 50 cm^3), dried and evaporated to give a pale yellow oil (3.4 g, 94%).

M.S. m/e (int. %), M^+ 267 (3), 256 (6), 149 (14), 106 (100), 78 (14).

I.R. ν_{max} cm^{-1}, 2250 (CN), 1520, 1350 (NO_2).

P.M.R. $\delta(CF_3CO_2H)$ ppm, 8.85 (2H, m, H-2'&6'), 8.39 (2H, d, $\underline{J}$=9H_z, H-3&5), 8.3 (1H, m, H-4'), 7.82-7.58 (2H, m, H-2&6), 7.42 (1H, m, H-5'), 4.67 (1H, d, $\underline{J}$=6H_z, NC-C$\underline{H}$-CH), 3.91 (1H, m, -CH-C$\underline{H}CH_3$), 1.71 (3H, d, $\underline{J}$=7.5H_z, $C\underline{H}_3$-CH).

Attempted dinitrations

(1) The above experiment was repeated at reflux. Tarry products were obtained.

(2) Repeating the experiment at 55° also gave tarry products.

(3) Fuming nitric acid was used instead and the nitrations attempted. As before the low temperature reaction afforded the mononitro derivative and increasing the temperature resulted in the formation of polymeric material.

(4) methylnitrate

To cooled (0°) stirred methanol (25 cm^3) concentrated sulphuric acid (9 cm^3) was cautiously added dropwise and the resulting solution was added to an ice cold well stirred nitrating mixture [fresh concentrated HNO_3 (50 cm^3), concentrated H_2SO_4 (50 cm^3)] keeping the temperature below 35°. A colourless organic layer separated. The organic layer was washed in the following sequence: brine (2 x 25 cm^3), brine + 3 drops of 30% sodium hydroxide (1 x 25 cm^3) and water (2 x 15 cm^3). Next the ester was dried over calcium chloride and used immediately.

Methylnitrate (25 cm^3) was added dropwise to an ice cold suspension of the nitrile (2 g) in concentrated sulphuric acid (25 cm^3) and stirred vigorously and allowed to warm to room temperature over two hours. The resulting pale yellow solution was poured on to crushed ice (150 g), basified and extracted with ethylacetate (5 x 50 cm^3), The combined extracts were dried and evaporated to give a viscous oil.

On standing a white solid separated (512 mg). The filtrate was found to be the mononitro derivative and the white solid as the corresponding amide.

m.p. 128°

M.S. m/e (int. %), M^+ 285 (50), 268 (21), 241 (17), 227 (25), 106 (100).

I.R.(P) ν_{max} cm^{-1}, 3300, 3200 ($CONH_2$), 1680, 1590 ($CONH_2$), 1595 (Py), 1520, 1350 (NO_2).

P.M.R. δ(d^6DMSO) ppm, 8.55 (1H, brs, H-2'), 8.40 (1H, bd, $J=7H_z$, H-6'), 8.25 (2H, d, $J=10H_z$, H-3&5), 7.8 (1H, m, H-4'), 7.75 (2H, d, $J=10H_z$, H-2&6), 7.34 (1H, m, H-5'), 6.68 (2H, brs, $CONH_2$),

3.95 (1H, d, J=12H_z, CO-CH-CH), 3.5 (1H, m, -CH-CH-CH_3), 0.92 (3H, d, J=8H_z, CH_3-CH). [Found: C, 63.0; H, 5.3; N, 14.6 $C_{15}H_{15}N_3O_3$ requires: C, 63.15; H, 5.3; N, 14.7%].

(5) acetylnitronium ion

Concentrated nitric acid (25 cm^3) was added dropwise to an ice cold suspension of the nitrile (2 g) in acetic anhydride (25 cm^3) and the mixture stirred for four hours at room temperature. Next it was poured on to crushed ice (150 g), basified and extracted with ethylacetate (3 x 100 cm^3), dried and evaporated to give an off white solid (1.6 g). Spectroscopic analysis confirmed initial TLC observations that it was unreacted starting material. This experiment was repeated with fuming nitric acid yielding an intractable gum.

(6) The above reaction using concentrated nitric acid was repeated at 55° and at reflux to afford tarry products.

5-Methoxy-1-nitrophenylacetic acid (88)

Diethyloxalate (22 g, 1 mol.eq.) was added in a stream to a cooled well stirred mixture of potassium ethoxide [potassium (5.8 g, 1 mol.eq.)] in absolute ethanol (25 cm^3) and dry ether (500 cm^3) under an atmosphere of nitrogen. After a lapse of fifteen minutes the nitroanisole (25 g, 1 mol.eq.) was added portionwise and left to stand over the weekend at room temperature.

The purple solid that had formed was collected, dissolved in cold 2% sodium hydroxide solution (500 cm^3) and treated with hydrogenperoxide (60 v/v, 200 cm^3). This mixture was stirred in the cold for three hours, filtered and the filtrate acidified to give an off white solid (15.6 g, 49%).

m.p. 173° (lit.[49], 176°).

U.V. λ_{max} n.m., 210, 234, 310.

I.R.(P) ν_{max} cm^{-1}, 3500 (COOH), 1720 (CO), 1615 (Ar), 1590, 1340 (NO_2).

P.M.R. $\delta(d^6DMSO)$ ppm, 8.12 (1H, brd, $\underline{J}$=8H_z, H-4), 7.08 (1H, brs, H-6), 7.05 (1H, d, $\underline{J}$=8H_z, H-3), 3.96 (2H, s, $C\underline{H}_2$-COO), 3.86 (3H, s, $C\underline{H}_3$-O).

5-Methoxyoxindole (89)

A solution of the nitrophenylacetic acid (10 g) in glacial acetic acid (100 cm^3) was hydrogenated (750 lb/sq inch) in the presence of 10% palladium on carbon (900 mg) for four hours at 80°. The resulting solution was filtered, and on evaporation a white solid was obtained (5.4 g, 70%).

m.p. 154° (lit.[106] 152-154°).

M.S. m/e (int. %), M^+ 163 (100), 148 (59).

U.V. λ_{max} n.m., 209. 255. 303.

I.R.(P) ν_{max} cm^{-1}, 3150, 3050 (NH), 1690 (CO), 1600 (Ar).

P.M.R. $\delta(CDCl_3)$ ppm, 9.76 (1H, brs, NH), 6.7 (3H, m, H-4,6&7), 3.7 (3H, s, $C\underline{H}_3$-O), 3.4 (2H, s, H-3).

3-[1-(3'-Pyridyl)ethylidene]-5-methoxyindolin-2-one (91)

Base catalysed reactions

(1) pyrrolidine

The oxindole (1.4 g, 1 mol.eq.), 3-acetylpyridine (1 g, 1 mol.eq.) and pyrrolidine (0.2 cm^3) was heated at reflux in dry benzene (30 cm^3) using a Dean-Stark apparatus for eight hours. On cooling crystalisation did not occur, therefore it was worked up for bases. TLC evidence, confirmed by spectroscopic analysis, showed the presence of unreacted starting material.

Changing the molar ratio of reactants, reaction temperature (toluene), catalyst concentration and the reaction time

systematically was equally fruitless.

(2) piperidine

The above experiment was repeated using piperidine but the result was the same.

(3) lithium diisopropylamide

A solution of the oxindole (1.4 g, 1 mol.eq.) in tetrahydrofuran (5 cm^3) was added dropwise to a cooled (-78°) stirred solution of lithium diisopropylamide (1 mol.eq.) in tetrahydrofuran (5 cm^3) and stirred under nitrogen for an hour. Next the acetylpyridine (1 g, 1 mol.eq.) was added and left to stir. Next day the mixture was worked up for bases.

Chromatographic and spectroscopic evidence showed it to be unreacted starting material.

(4) lithium dicyclohexylamide

The above experiment was repeated using lithium dicyclohexylamide but with a similar result.

Acid catalysed reaction

(5) ethanolic hydrochloric acid

The oxindole (10 g, 1 mol.eq.) and 3-acetylpyridine (7.4 g, 1 mol.eq.) were heated at reflux in ethanolic hydrochloric acid (75 cm^3). An orange precipitate was formed within an hour, but the heating was continued for a further hour before cooling the contents. The hydrochloric salt was collected, dissolved in water (100 cm^3) and basified, whereupon the free base was collected as an orange solid (12.3 g, 80%).

m.p. 155°.

M.S. m/e (int. %), M^+ 266 (100), 251 (30).

I.R.(P) ν_{max} cm^{-1}, 3450, 3160 (NH), 1700 (CO), 1600 (Ar).

P.M.R. $\delta(CDCl_3)$ ppm, 9.65 (1H, brs, NH), 8.5 (2H, m, H-2'&6'), 7.65 (1H, m, H-4'), 7.48, 7.28 (1H, dd, $\underline{J}_1=\underline{J}_2=6H_z$, H-5'), 7.18 (1H, brs, H-7), 6.78 (2H, brs, H-4&6), 3.8 (3H, s, $C\underline{H}_3$-O), 2.6 (3H, s, $C\underline{H}_3$-).

3-[1-(3'-Pyridyl)ethyl]-5-methoxyindolin-2-one (92)

The product from the previous experiment (12 g) and sodium borohydride (5 g) were boiled in ethanol (100 cm^3) for an hour, cooled and poured on to crushed ice (250 g). Then it was extraxted with dichloromethane (5 x 200 cm^3), dried and evaporated to give a viscous oil/gum (12.5 g, 98%).

3-[1-(3'-Pyridyl)ethyl]-2-chloro-5-methoxyindole (93)

The pyridyloxindole from the previous experiment (7.2 g, 1 mol.eq.) and phosphorus oxychloride (8.3 g, 2 mol.eq.) were heated at reflux for five hours under an atmosphere of nitrogen. The cooled reaction mixture was poured on to crushed ice (500 g), basified and extracted with hot ethylacetate (20 x 75 cm^3). The combined extracts were dried and evaporated to give a dark oil, which solidified on standing.

This was re-crystallised from ethanol (4.7 g, 60%).

m.p. 120°.

M.S. m/e (int.%), M^+ 286 (43), 271 (64), 252 (64), 237 (100), 107 (57).

U.V. λ_{max} n.m., 210, 265.

I.R.(P) ν_{max} cm^{-1}, 3400, 3250 (NH), 1620 (Ar), 1580 (Py).

P.M.R. $\delta(d^6DMSO)$ ppm, 12.48 (1H, brs, NH), 8.6 (1H, d, $\underline{J}=2H_z$, H-2'), 8.38 (1H, bd, $\underline{J}=6H_z$, H-6'), 7.72 (1H, m, H-4'), 7.28, 7.22 (1H, dd, $\underline{J}_1=\underline{J}_2=6H_z$, H-5'), 7.25 (1H, d, $\underline{J}=8H_z$, H-7), 6.9 (1H, d, $\underline{H}=2H_z$, H-4), 6.8, 6.52 (1H, dd, $\underline{J}=2H_z$, $\underline{J}=8H_z$, H-6), 4.5 (1H, q,

J=8H$_z$, CH-CH$_3$), 3.68 (3H, s, CH$_3$-O), 1.76 (3H, d, J=8H$_z$, CH-CH$_3$).

Attempted dehalogenation of the pyridylethylchloroindole

Hydrogenations over various catalysts

(1) 10% palladium on carbon

A solution of the chloro compound (1 g) in absolute ethanol (25 cm^3) and a few drops of triethylamine was hydrogenated (80 lb/sq inch) over 10% palladium on carbon (0.5 g) for five hours. On work up unreacted starting material was returned.

The above experiment was repeated many times, systematically increasing the catalyst content, the hydrogen pressure and the reaction time. Eventually, the chloro compound (1 g), 10% palladium on carbon (2.5 g) and a few drops of triethylamine in absolute ethanol (25 cm^3) were hydrogenated (1200 lb/sq inch) over the weekend. On work up, chromatographic analyses showed a trace of a compound slower than the starting material and comparison with an authentic sample confirmed the slower compound to be the dehalogenated product.

(2) W2 Raney Nickel

The above experiment was repeated with raney nickel but the result was the same.

(3) sodium cyanoborohydride

Excess sodium cyanoborohydride (2 g) was added portionwise to a stirred solution of the chloro compound (1 g) in glacial acetic acid (25 cm^3) under a nitrogen atmosphere. The mixture was stirred at room temperature for two hours then an hour at 60° and left to stir at room temperature.

Next day the contents were poured on to crushed ice, basified and stirred at pH 14 for thirty minutes. Then the reaction mixture

was extracted with dichloromethane (3 x 50 cm^3), dried and evaporated to give a red viscous oil (1.2 g). TLC showed it to be starting material.

(4) tetrabutylammonium borohydride

To a suspension of tetrabutylammonium bisulphate (6 g) in water (5 cm^3), 5 M sodium hydroxide (4 cm^3) was added and cooled to room temperature. To this, a solution of sodium borohydride (0.7 g, 1.1 mol.eq.) in water (3 cm^3) was added and stirred for ten minutes. The reaction mixture was extracted with dichloromethane (3 x 50 cm^3), dried over anhydrous potassium carbonate and evaporated to give a white solid.

I.R. ν_{max} cm^{-1}, 2300-2100 (BH).

To this solid, the chloroindole (1.5 g, 1/3 mol.eq.) was added and heated at reflux in dry dichloromethane (50 cm^3) for fifteen hours. On evaporation an amber oil was obtained. Chromatographic analysis indicated it to be a multi-component mixture.

2-(3'-Pyridyl)imidazoline (96)

3-Cyanopyridine (35 g, 1 mol.eq.) and 1,2-diamino ethane (22 cm^3, 1 mol.eq.) was stirred at 100° in the presence of sulphur (1 g) for three hours. An initial green solution gradually turned brown. On cooling it solidified. Re-crystallised from acetonitrile as white needles (45.8 g, 90%).

m.p. 53° (lit.[76] 54°).

U.V. λ_{max} n.m., 205, 222, 270.

P.M.R. $\delta(d^6DMSO)$ ppm, 8.95 (1H, d, $\underline{J}=2H_z$, H-2), 8.62, 8.58 (1H, dd, $\underline{J}=2H_z$, $\underline{J}=4H_z$, H-6), 8.15 (1H, m, H-4), 7.48, 7.4 (1H, dd, $\underline{J}_1=\underline{J}_2=4H_z$, H-5), 4.8 (1H, brs, NH), 3.64 (4H, s, $-\underline{CH_2}\underline{CH_2}-$).

3'-(Indol-3-ylformyl)pyridine (95)

Indole (11.7 g, 1 mol.eq.) and pyridine-3-imidazole (14.7 g, 1 mol.eq.) were dissolved in acetic anhydride (35 cm^3) and left to stand. Next day the adduct was collected by decanting the solvent (26 g, 98%).

I.R.(P) ν_{max} cm^{-1}, 3150, 3100 (NH), 1680, 1650 (Ac), 1590 (Py).

This solid (5 g) and sodium hydroxide (1 g) were boiled in ethanol (25 cm^3) and water (5 cm^3) for two hours, cooled and poured on to crushed ice (100 g). On standing a white solid settled. Re-crystallised from methanol (2.8 g, 80%).

m.p. 210-211° (lit.[49] 210°).

M.S. m/e (int. %) $M^{+\cdot}$ 222 (80), 144 (100), 117 (60).

U.V. λ_{max} n.m., 230, 258, 270, 320.

I.R.(P) ν_{max} cm^{-1}, 3150 (NH), 1590 (CO), 1580 (Py).

P.M.R. δ(d^6DMSO) ppm, 12.10 (1H, brs, NH), 9.05 (1H, d, $\underline{J}=2H_z$, H-2'), 8.80, 8.72 (1H, dd, $\underline{J}=2H_z$, $\underline{J}=6H_z$, H-6'), 8.50-7.92 (3H, m, H-4'2&4), 7.81-7.12 (4H, m, H-5',5,6&7).

3'-(5-Methoxyindol-3-ylformyl)pyridine (95a)

The above experiment was repeated with 5-methoxyindole to obtain the title compound in 80% yield.

m.p. 182°.

M.S. m/e $M^{+\cdot}$ 252 (100).

U.V.λ_{max} n.m., 232, 256, 270, 318.

I.R.(P) ν_{max} cm^{-1}, 3150 (NH), 1590 (CO), 1580 (Py).

P.M.R. δ(d^6DMSO) ppm, 12.8 (1H, brs, NH), 9.0 (1H, d, $\underline{J}=2H_z$, H-2'), 8.8, 8.72 (1H, dd, $\underline{J}=2H_z$, $\underline{J}=6H_z$, H-6'), 8.2 (1H, m, H-4'), 8.0 (1H, s, H-2), 7.9 (1H, d, $\underline{J}=2H_z$, H-4), 7.6-7.45 (1H, dd, $\underline{J}_1=\underline{J}_2=6H_z$, H-5'), 7.5 (1H, d, $\underline{J}=8H_z$, H-7), 7.01, 6.92 (1H, dd, $\underline{J}=2H_z$, $\underline{J}=8Hz$, H-6), 3.88 (3H, s, $C\underline{H}_3$-O).

3'-(1-Benzenesulphonylindol-3-ylformyl)pyridine (98)

A solution of the indole (5 g, 1 mol.eq.) in dry dimethylsulphoxide (20 cm^3) was added dropwise to a stirred suspension of dimsyl sodium [sodium hydride (2.25 g, 1.1 mol.eq.)] in dry dimethylsulphoxide (10 cm^3) under a nitrogen atmosphere and stirred for an hour. To the resulting pale yellow solution benzenesulphonyl chloride (8.6 g, 1.1 mol.eq.) was added and stirred for another hour before pouring on to crushed ice (150 g) whereupon a white solid formed.

Re-crystallised from ethanol (5.3 g, 65%).

m.p. 110°.

M.S. m/e $M^{\dagger}$ 362.

I.R.(P) ν_{max} cm^{-1}, 1630 (CO), 1570 (Py).

P.M.R. $\delta(d^6DMSO)$ ppm, 9.15 (1H, s, H-2'), 8.9 (1H, d, $\underline{J}=4H_z$, H-6'), 8.5 (1H, s, H-2), 8.4-8.18 (4H, m,), 8.08 (1H, m, H-4'), 7.8-7.52 (5H, m), 7.5-7.45 (1H, dd, $\underline{J}_1=\underline{J}_2=4H_z$, H-5').

3'-(1-Benzenesulphonyl-5-methoxyindol-3-ylformyl)pyridine (98a)

The above experiment was repeated with the corresponding 5-methoxyindole analogue to give the title compound in 62% yield.

m.p. 156°.

M.S. m/e $M^{\dagger}$ 392.

I.R.(P) ν_{max} cm^{-1}, 1620 (CO), 1520 (Py).

P.M.R. $\delta(d^6DMSO)$ ppm, 9.1 (1H, brs, H-2'), 8.9 (1H, brs, H-6'), 8.4 (1H, s, H-2), 8.44-7.6 (9H, m), 7.15, 7.06 (1H, dd, $\underline{J}=2H_z$, $\underline{J}=8H_z$, H-6), 3.85 (3H, s, $C\underline{H}_3$-O).

Reaction at the carbonyl function in (98) and (98a) dimethylsulphonium methylide (99)

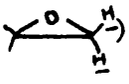
A solution of trimethylsulphonium iodide (3.8 g, 1.2 mol.eq.) in dry dimethylsulphoxide (25 cm^3) was added dropwise to a cooled

(-10°) well stirred solution of dimsyl sodium [sodium hydride (0.89 g, 1.2 mol.eq.), dimethylsulphoxide (10 cm^3)] in tetrahydrofuran (50 cm^3) under nitrogen. To the ensuing suspension a solution of indole (5.6 g, 1 mol.eq.) in dry dimethylsulphoxide (25 cm^3) was added and stirred for twenty minutes at -10° before allowing to warm to room temperature over an hour.

Next the pale green solution was poured on to crushed ice (300 g) and washed with petrol (3 x 50 cm^3). The aqueous phase separated and extracted with dichloromethane (5 x 150 cm^3). The combined organic extracts were washed with water (3 x 50 cm^3) and dried over anhydrous potassium carbonate. On evaporation an off white solid was obtained. (3.7 g).

TLC analysis showed a mixture of compounds, one of which corresponded to 3-pyridyl indolyl ketone.

I.R. ν_{max} cm^{-1}, 1590 [CO of (95)], 1570 (Py).

P.M.R. $\delta(d^6DMSO)$, 3.6 (2H, dd, ).

Changing the molar ratios of reactants, temperature and reaction time did not change the composition of the final product.

The above experiment was repeated with the corresponding 5-methoxy analogue with the same result.

Ethyl 3-(1-benzenesulphonylindol-3-yl)-3-(3'-pyridyl)propenoate (100)

Triethylphonoacetate (3.7 g, 1.2 mol.eq.) was added dropwise to a cooled well stirred suspension of sodium hydride (0.8 g, 1.2 mol.eq.) in dry tetrahydrofuran (25 cm^3) under nitrogen and stirred until gas evolution ceased. Then the indole (5 g, 1 mol.eq.) in dry tetrahydrofuran (50 cm^3) was added dropwise and left to stir. Next day the pale orange solution was poured

on to crushed ice (300 g). On standing a solid formed.

Re-crystallised from methanol (4.9 g, 80%).

m.p. 123°.

M.S. m/e M^{+} 432.

U.V. λ_{max} (ε) n.m., 216 (40,390), 256 (19,980), 308 (18,430).

I.R.(P) ν_{max} cm^{-1}, 1700 (CO), 1600 (Ar), 1590 (Py).

P.M.R. δ($CDCl_3$) ppm, 8.65 (1H, brd, J=6H_z, H-6'), 8.5 (1H, brs, H-2'), 8.0-7.2 (12H, m), 6.56 (1H, s, C<u>H</u>=), 4.05 (2H, q, J=8H_z, $C\underline{H}_2$-CH_3), 1.1 (3H, t, J=8H_z, C<u>H</u>-CH_2). [Found: C, 66.0; H, 4.5; N, 6.5 $C_{24}H_{20}H_2O_4S$ requires: C, 66.7; H, 4.7; N, 6.5%].

<u>3-(1-Benzenesulphonylindol-3-yl)-3-(3'-pyridyl)propenonitrile (101)</u>

The diethylphosphonoacetonitrile (5.9 g, 1.2 mol.eq.) was added dropwise to a cooled well stirred suspension of sodium hydride (1.6 g, 1.2 mol.eq.) in dry tetrahydrofuran (10 cm^3) under nitrogen and stirred until the gas evolution ceased. Then the indole (10 g, 1 mol.eq.) in tetrahydrofuran (50 cm^3) was added and left to stir. Next day the dark solution was poured on to crushed ice (300 g) and on standing a solid settled. Re-crystallised from methanol (9.3 g, 86%).

m.p. 156°.

M.S. m/e M^{+} 386.

U.V. λ_{max} (ε) n.m., 217 (23,050), 256 (12,420), 315 (11,890).

I.R.(P) ν_{max} cm^{-1}, 2200 (CN), 1639 (C=C), 1590 (Py).

P.M.R. δ(d^6DMSO) ppm, 8.8 (2H, m, H-2'&6'), 8.2-7.2 (12H, m), 6.6 (1H, s, -C<u>H</u>=). [Found: C, 68.6; H, 3.9; N, 11.0 $C_{22}H_{15}N_3O_2S$ requires: C, 68.6; H, 3.9; N, 10.9%].

<u>Ethyl 3-pyridyl-glycidate (110)</u>

Potassium tertiary butoxide (11.2 g, 1.2 mol.eq.) was added

portionwise to a cooled solution of 3-acetylpyridine (10 g, 1 mol.eq.) and ethylchloroacetate (10.2 g, 1 mol.eq.) in dry benzene (50 cm^3) and the reaction mixture stirred for two hours.

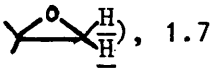
A thick paste was formed which gradually turned pink. On pouring on to crushed ice (300 g) and extraction with dichloromethane (3 x 100 cm^3) afforded an oil. Chromatographic analysis showed it to be unreacted starting material.

The experiment was repeated using ^tBuOK in ^{t}butanol, sodium amide, sodium ethoxide and potassium amide with a similar result.

1-Methyl-1-(3'-pyridyl)oxirane (112)

A solution of trimethylsulphonium iodide (20.3 g, 1.2 mol.eq.) in dry dimethylsulphoxide (90 cm^3) was added to a cooled (-10°) well stirred suspension of dimsyl sodium [sodium hydride (4.8 g, 1.2 mol.eq.), dimethylsulphoxide (10 cm^3)] in dry tetrahydrofuran (100 cm^3) under a nitrogen atmosphere. Then the pyridyl ketone (10 g, 1 mol.eq.) was added and stirred in the cold (-10°) for an hour before allowing the reaction mixture to warm to room temperature. The resulting pale green solution was poured into iced water (600 cm^3) and washed with petrol (3 x 50 cm^3). The aqueous phase separated and extracted with dichloromethane (5 x 150 cm^3). The combined extracts were washed with water (5 x 50 cm^3), dried over anhydrous potassium carbonate and evaporated to give a pale orange oil (10.6 g, 95%).

U.V. λ_{max} n.m., 213, 260, 266, 273.

P.M.R. $\delta(CDCl_3)$ ppm, 8.6 (1H, d, $\underline{J}=2H_z$, H-2), 8.6, 8.47 (1H, dd, $\underline{J}=2H_z$, $\underline{J}=8H_z$, H-6), 7.6 (1H, m, H-4), 7.22, 7.15 (1H, dd, $\underline{J}_1=\underline{J}_2=8H_z$, H-5), 2.95, 2.75 (2H, dd, $\underline{J}_1=\underline{J}_2=6H_z$, ), 1.7 (3H, s, CH_3).

3-Hydroxy-3-(3'-pyridyl)butyronitrile (114)

Potassium cyanide (9.6 g, 2 mol.eq.) was added portionwise to a cooled solution of magnesium sulphate (18 g, 2 mol.eq.) in water (100 cm^3) and stirred for an hour. To the resulting opaque suspension the oxirane (10 g, 1 mol.eq.) was added dropwise and left to stir at room temperature over the weekend. The dark reaction mixture was poured into water (250 cm^3) and extracted with ethylacetate (10 x 75 cm^3). The combined extracts were washed with water (3 x 50 cm^3), dried and evaporated to give a brown oil (11 g, 93%).

U.V. λ_{max} n.m., 208, 255, 260, 266.

I.R.(L) ν_{max} cm^{-1}, 3200 (OH), 2250 (CN), 1595 (Py).

P.M.R. $\delta(CDCl_3)$ ppm, 8.75 (1H, d, $\underline{J}=2H_z$, H-2), 8.45 (1H, brd, $\underline{J}=6H_z$, H-6), 7.95 (1H, brd, $\underline{J}=8H_z$, H-4), 7.4, 7.3 (1H, dd, $\underline{J}_1=\underline{J}_2=8H_z$, H-3), 6.32 (1H, brs, -OH), 2.9 (2H, s, $-CH_2-$), 1.75 (3H, s, CH_3).

Attempted dehydration of the hydroxy nitrile

(1) concentrated hydrochloric acid

The hydroxy nitrile (2 g) and concentrated hydrochloric acid (10 cm^3) were stirred at room temperature for six hours and then worked up for bases. Chromatographic analysis showed unreacted starting material.

The above experiment was repeated, but heated at reflux for six hours with the same result.

(2) 4-toluenesulphonic acid

The hydroxy nitrile (2 g, 1 mol.eq.), 4-toluenesulphonic acid (2.6 g, 1.1 mol.eq.) were heated at reflux for three hours in dry benzene (50 cm^3) under Dean-Stark conditions. On work up

for bases and TLC analysis showed unreacted starting material. Increasing the amount of acid and the reaction time was equally fruitless.

(3) 4-toluenesulphonyl chloride and triethylamine

The hydroxy nitrile (2 g, 1 mol.eq.), 4-toluenesulphonyl chloride (4.7 g, 2 mol.eq.) and triethylamine (1 g) were dissolved in dichloromethane (25 cm^3) and stirred at 0° for three hours. On work up for bases starting material was obtained.

Increasing the reaction time and temperature, changing the base to sodium carbonate and the solvent to tetrahydrofuran were equally unsuccessful.

Attmepted protection of the alcohol

Dihydropyran (2 g, 2 mol.eq.) was added dropwise to a solution of the nitrile (2 g, 1 mol.eq.) and 4-toluenesulphonic acid (2.8 g, 1.2 mol.eq.) in dichloromethane (25 cm^3). An initial pink colouration darkened to green with stirring. The reactants were stirred for two hours at room temperature, then dried over anhydrous potassium carbonate and evaporated to give an oil. TLC analysis showed it contained only unreacted starting material.

Attempted reduction to the aldehyde

Hydrogenchloride gas was bubbled to anhydrous stannous chloride (7.4 g, 1.5 mol.eq.) in dry ether (50 cm^3) until all the stannous chloride had dissolved. To this suspension the hydroxy nitrile (3.5 g, 1 mol.eq.) was added all at once. A brownish precipitate formed at once. This was mechanically stirred for thirty minutes before the addition of water (50 cm^3), basified and extracted with dichloromethane (5 x 100 cm^3). The combined extracts were dried and evaporated to give an oil

Chromatography and spectroscopy showed it to be unreacted starting material.

3-(3'-Pyridyl)but-2-encarbonitrile (115)

Phosphorus tribromide (5 cm^3) was added dropwise to a cooled stirred solution of the nitrile (1 g) in dry dichloromethane (10 cm^3) and stirred at room temperature for five hours. Excess reagent and solvent evaporated, the residue dissolved in ice water (50 cm^3), basified and stirred with potassium hydroxide (0.5 g) for an hour before extracting with dichloromethane (3 x 50 cm^3), dried and evaporated to give an oil (0.8 g, 90%).

U.V. λ_{max} n.m., 205, 255.

I.R.(L) ν_{max} cm^{-1}, 2200 (CN), 1610 (C=C), 1585 (Py).

P.M.R. $\delta(CDCl_3)$ ppm, 8.72 (1H, d, $\underline{J}=2H_z$, H-2), 8.61, 8.56 (1H, dd, $\underline{J}=2H_z$, $\underline{J}=8H_z$, H-6), 7.83 (1H, m, H-4), 7.4, 7.32 (1H, dd, $\underline{J}_1=\underline{J}_2=8H_z$, H-5), 5.76 (1H, q, $\underline{J}=1.1H_z$, C=$\underline{CH}$-CN, NOE-ve), 5.58 (1H, q, $\underline{J}=1.3H_z$, C=$\underline{CH}$CN, NOE+ve), 2.42 (3H, d, $\underline{J}=1.1H_z$, CH_3-C), 2.30 (3H, d, $\underline{J}=1.3H_z$), $\underline{E}$-:$\underline{Z}$- (1:0.81).

The above experiment was repeated using thionyl chloride. On base work up an oil was obtained which solidified on standing. re-crystallised from methanol (94%).

m.p. 49°.

M.S. m/e (int. %), M^+ 140 (100), 117 (20), 104 (27), 79 (27).

U.V. λ_{max} n.m., 205, 255.

I.R.(P) ν_{max} cm^{-1}, 2200 (CN), 1610 (C=C), 1585 (Py).

P.M.R. $\delta(CDCl_3)$ ppm, 8.72 (1H, d, $\underline{J}=2H_z$, H-2), 8.61 8.56 (1H, dd, $\underline{J}=2H_z$, $\underline{J}=8H_z$, H-6), 7.83 (1H, m, H-4), 7.4, 7.32 (1H, dd, $\underline{J}_1=\underline{J}_2=8H_z$, H-5), 5.76 (1H, q, $\underline{J}=1.1H_z$, C=CH-CN, NOE-ve), 5.58 (1H, q, $\underline{J}=1.3H_z$, C=CH-CN, NOE+ve), 2.42 (3H, s, CH_3-C), 2.30 (3H, s,

CH_3-C), E-:Z- (18:1). [Found C, 74.9; H, 5.4; N, 18.9 $C_9H_8N_2$ requires: C, 75.0; H, 5.55; N, 19.4%].

3-(3-Pyridyl)butanocarbonitrile (116)

The nitrile (1 g) and excess sodium borohydride (2 g) in absolute ethanol (25 cm^3) was stirred at 60° for two hours, cooled and poured on to crushed ice (150 g) and extracted with dichloromethane (3 x 100 cm^3), dried and evaporated to give a yellow oil (0.9 g, 94%).

U.V. λ_{max} n.m., 207, 250, 255, 262, 267, 295.

I.R.(L) ν_{max} cm^{-1}, 2224 (CN), 1595 (Py).

P.M.R. $\delta(CDCl_3)$ ppm, 8.55 (1H, d, $J=2H_z$, H-2), 8.48 (1H, bd, H-6), 7.65 (1H, m, H-4), 7.3, 7.23 (1H, dd, $J_1=J_2=8H_z$, H-5), 3.24 (1H, m, CH_3-CH-CH_2), 2.69 (2H, d, $J=8H_z$, CH_2-CN), 1.45 (3H, d, $J=10H_z$, CH_3-CH).

3-(3'-Pyridyl)butanol (117)

(1) lithium triethoxyaluminiumhydride

Freshly distilled dry ethylacetate (5 g, 1.5 mol.eq.) was added dropwise to a cooled (0°) stirred solution of lithium aluminiumhydride (1.4 g, 1.1 mol.eq.) in dry ether (50 cm^3) under an atmosphere of nitrogen. After a lapse of fifteen minutes the nitrile (5 g, 1 mol.eq.) was added, an exothermic reaction occurred followed by the formation of a brown solid. Stirring was continued at room temperature for a further thirty minutes before the addition of 2M sulphuric acid (10 cm^3), basified and extracted with dichloromethane (5 x 75^3). The combined extracts were dried and evaporated to give an oil (4.6 g). TLC showed a new slower component and starting material.

I.R.(L) ν_{max} cm^{-1}, 2224(CN), 1720 (CO), 1595 (Py).

P.M.R. $\delta(CDCl_3)$ ppm, 9.85 (1H, brs, -CHO), 8.55 (1H, d, J=2H$_z$, H-2), -CHO:H-2 (0.3:1).

(2) diisobutylaluminiumhydride

A solution of diisobutylaluminiumhydride (1.2 M, 7.2 cm^3, 1.2 mol.eq.) was added dropwise to a cooled well stirred solution of the nitrile (1 g, 1 mol.eq.) in dry toluene (10 cm^3) under nitrogen. An exothermic reaction occurred, and the resulting darkened solution was stirred for a further ninety minutes at room temperature before pouring on to crushed ice (50 g). This mixture was then extracted with dichloromethane (5 x 50 cm^3), the combined extracts dried and evaporated to give an oil identical in all respects (TLC and spectroscopy) with the previous reduction product.

A 40% redution was recorded.

(3) Stephens' reduction

Hydrogenchloride gas was bubbled into anhydrous stannous chloride (7 g, 1.5 mol.eq.) in dry ether (50 cm^3) until all the stannous chloride dissolved. To this suspension the nitrile (3.5 g, 1 mol.eq.) in ether (25 cm^3) was added all at once. Immediately a brownish buff precipitate formed and mechanical stirring continued for another thirty minutes. Next it was dissolved in water (50 cm^3), basified and extracted with dichloromethane (5 x 100 cm^3), dried and evaporated to give an oil.

TLC analysis showed it to be unreacted starting material.

Ethyl 3-(3'-pyridyl)but-2-enoate (128)

Triethylphosphonoacetate (41 g, 1.5 mol.eq.) was added dropwise to a cooled stirred suspension of sodium hydride (9 g, 1.5 mol.eq.) in tetrahydrofuran (75 cm^3) under nitrogen and stirred until the

gas evolution ceased. Then the acetylpyridine (15 g, 1 mol.eq.) was added dropwise and the ensuing pale green solution was left stirring over the weekend. The resulting dark red solution was poured on to crushed ice (300 g) and extracted with dichloromethane (7 x 100 cm^3), the combined extracts dried and evaporated to give an amber oil (22 g, 94%).

U.V. λ_{max} n.m., 217, 257.

I.R.(L) ν_{max} cm^{-1}, 1715 (CO), 1630 (C=C), 1585 (Py).

P.M.R. $\delta(CDCl_3)$ ppm, 8.75 (1H, d, $\underline{J}=2H_z$, H-2), 8.6 (1H, brd, $\underline{J}=6H_z$, H-6), 7.8 (1H, m, H-4), 7.35, 7.28 (1H, dd, $\underline{J}_1=\underline{J}_2=6H_z$, H-3), 6.16 (1H, q, $\underline{J}=1H_z$, C=CH-), 4.23 (2H, q, $\underline{J}=8H_z$, $C\underline{H}_2-CH_3$), 2.6 (3H, d, $\underline{J}=1H_z$, $CH_3C=CH-$), 1.32 (3H, t, $\underline{J}=8H_z$, $C\underline{H}_3-CH_2$).

Ethyl 3-(3'-pyridyl)butanoate (129)

A solution of the pyridine ester (10 g) in ethanol (100 cm^3) was hydrogenated (100 lb/sq inch) over 10% palladium on carbon (1 g) at room temperature for fifteen hours. Filtration and evaporation afforded an oil (10 g, 98%).

U.V. λ_{max} n.m., 215, 258, 264, 271.

I.R.(L) ν_{max} cm^{-1}, 1738 (CO), 1590, 1580 (Py).

P.M.R. $\delta(CDCl_3)$ ppm. 8.5 (1H, d, $\underline{J}=2H_z$, H-2), 8.49, 8.41 (1H, dd, $\underline{J}=2H_z$, $\underline{J}=6H_z$, H-6), 7.55 (1H, m, H-4), 7.25, 7.18 (1H, dd, $\underline{J}_1=\underline{J}_2=6H_z$, H-5), 4.1 (2H, q, $\underline{J}=8H_z$, $C\underline{H}_2-CH_3$), 3.3 (1H, m, $CH_3-\underline{CH}-CH_2-$), 2.58 (2H, d, $\underline{J}=7H_z$, $-CH-\underline{CH}_2-$), 1.3 (3H, d, $\underline{J}=8H_z$, $C\underline{H}_3-CH$), 1.15 (3H, t, $\underline{J}=8H_z$, $C\underline{H}_3-CH_2$).

3-(3'-Pyridyl)butanal (117)

A solution of diisobutylaluminium hydride (1.2 M, 65 cm^3, 1.5 mol.eq.) was added dropwise to a cooled (-78°) well stirred solution of the pyridine ester (10 g, 1 mol.eq.) in dry toluene

($20\ cm^3$) under nitrogen. Effervescence subsided to give a greenish yellow viscous solution that was stirred for a further two hours at -78°). Then the complex acetal was hydrolysed by the addition of water ($20\ cm^3$) and extracted with dichloromethane ($7 \times 150\ cm^3$). The combined extracts were dried and evaporated to give a pale yellow oil (7.2 g, 93%).

I.R.(L) $\nu_{max}\ cm^{-1}$, 2720 (C<u>H</u>O), 1720 (CO), 1590, 1570 (Py).

P.M.R. $\delta(CDCl_3)$ ppm, 9.60 (1H, d, <u>J</u>=$1H_z$, CH_2-C<u>H</u>O), 8.46 (1H, d, <u>J</u>=$2H_z$, H-2), 8.42, 8.38 (1H, dd, <u>J</u>=$2H_z$, <u>J</u>=$6H_z$, H-6), 7.49 (1H, m, H-4), 7.2, 7.12 (1H, dd, $\underline{J}_1=\underline{J}_2=6H_z$, H-5), 3.32 (1H, m, CH_3-C<u>H</u>-CH_2), 2.68 (2H, brd, <u>J</u>=$8H_z$, CH-C<u>H</u>$_2$-CHO), 1.26 (3H, d, <u>J</u>=$6H_z$, C<u>H</u>$_3$-CH).

<u>3-[1-(3'-Pyridyl)ethyl]indole (53)</u>

Phenylhydrazine hydrochloride (4.9 g, 1 mol.eq.), pyridine butanal (5 g, 1 mol.eq.) in ethanol ($150\ cm^3$) was maintained at gentle reflux on a steam bath for four hours (TLC suggested complete reaction within fifteen minutes). Cooled and evaporated to give a red oil, which was treated with ethanolic hydrochloric acid ($100\ cm^3$) and heated at reflux for ninety minutes. The initial pale orange solution turned pale green then darkened with time. On cooling ammonium chloride crystallised out ($AgNO_3/NH_4OH$ and +ve test for NH_3 on heating). The cooled reaction mixture was evaporated and the residue dissolved in iced water ($200\ cm^3$), basified and extracted with dichloromethane ($5 \times 100\ cm^3$). The combined extracts were dried and evaporated to give an off white solid. Re-crystallised from methanol (4.3 g, 56%).

m.p. 172° (lit.[44], 173°).

M.S. m/e (int. %) M^+ 222 (60), 207 (100), 144 (20).

U.V. λ_{max} n.m., 204, 219, 257, 292.

I.R.(P) ν_{max} cm^{-1}, 3140 (NH), 1620 (Ar), 1590, 1580 (Py).

P.M.R. $\delta(CDCl_3)$ ppm, 8.7 (1H, brs, NH), 8.6 (1H, d, $\underline{J}$=2H_z, H-2'), 8.41, 8.36 (1H, dd, $\underline{J}$=2H_z, $\underline{J}$=6H_z, H-6'), 7.6-6.9 (7H, m,), 4.4 (1H, q, $\underline{J}$=8H_z, $C\underline{H}CH_3$), 1.7 (3H, d, $\underline{J}$=6H_z, $C\underline{H}_3CH$).

Using the same technique, 4-methoxy, 3-fluoro, 3-methyl, 2-fluoro, 2-methyl and 2-chlorophenylhydrazines were reacted with 3-(3'-pyridyl)butanal to afford the corresponding pyridylethyl indoles in 45-55% yield.

3-[1-(3'-Pyridyl)ethyl]-5-methoxy indole (139, R=5-MeO)

m.p. 136-7°.

M.S. m/e (int. %) M^+ 252 (100), 237 (62).

U.V. λ_{max} (ε) n.m., 220 (25,940), 268 (7,660), 297 (5,360), 308 (3,890).

I.R.(P) ν_{max} cm^{-1}, 3180, 3160 (NH), 1620 (Ar), 1580, 1570 (Py).

P.M.R. $\delta(d^6DMSO)$ ppm, 10.80 (1H, brs, N$\underline{H}$), 8.61 (1H, d, $\underline{J}$=2H_z, H-2'), 8.41, 8.36 (1H, dd, $\underline{J}$=2H_z, $\underline{J}$=6H_z, H-6'), 7.66 (1H, m, H-4'), 7.38-7.18 (3H, m, H-4,6&7), 6.83-6.65 (2H, m, H-5'&2), 4.36 (1H, q, $\underline{J}$=8H_z, $\underline{CH}$-CH_3), 3.66 (3H, s, $\underline{CH}_3$-O), 1.68 (3H, d, $\underline{J}$=8H_z, $\underline{CH}_3$-CH).

^{13}C.M.R. $\delta(d^6DMSO)$ ppm, C-2, 123.2; C-3, 118.4; C-3a, 126.7; C-4, 112.1; C-5, 153.0; C-6, 101.2; C-7, 111.0; C-7a, 142.3; C-8, 33.9; C-9, 21.8; C-1', 148.9; C-3', 147.0; C-4', 122.7; C-5', 134.5; C-6', 132.0; MeO, 55.4. [Found: C, 76.0; H, 6.4; N, 11.2; $C_{16}H_{16}N_2O$ requires: C, 76.2; H, 6.4; N, 11.11%].

3-[1-(3'-Pyridyl)ethyl]-(6&4)-fluoroindole (139, R=6-F, 4-F)

P.M.R. $\delta(d^6DMSO)$ ppm, 12.15 (1H, brs, N$\underline{H}$), 11.94 (1H, brs, N$\underline{H}$), 8.58 (1H, d, $\underline{J}$=2H_z, H-2'), 8.50 (1H, d, $\underline{J}$=2H_z, H-2'), 8.35 (2H, brd, $\underline{J}$=6H_z, 2 x H-6'), 7.7-7.5 (2H, m, 2 x H-4'), 7.4-6.5 (10H, m,),

4.5 (2H, m, CH-CH_3), 1.7 (6H, d, J=8H_z, CH_3-CH).

No change on increasing the temperature.

3-[1-(3'-Pyridyl)ethyl]-(6&4)-methylindole (139, R=6-Me, 4-Me)

P.M.R. δ(d^6DMSO) ppm, 11.02 (1H, brs, NH), 10.65 (1H, brs, NH), 8.50 (1H, d, J=2H_z, H-2'), 8.38 (1H, d, J=2H_z, H-2'), 8.30 (2H, brd, J=6H_z, 2 x H-6'), 7.62-7.4 (2H, m, 2 x H-4'), 7.3-6.5 (10H, m), 4.65 (1H, q, J=8H_z, CH-CH_3), 4.35 (1H, q, J=8H_z, CH-CH_3), 2.35 (6H, 2 x CH_3-Ar), 1.64 (64, d, J=8H_z, 2 x CH_3-CH).

No change on heating.

3-[1-(3'-Pyridyl)ethyl]-7-fluoroindole (139, R=7-F)

m.p. 162°.

M.S. m/e (int. %), M^+ 240 (60), 225 (100).

U.V. λ_{max} (ε) n.m., 215 (51,490), 262 (11,840), 287 (5,840).

I.R.(P) ν_{max} cm^{-1}, 3410, 3100 (NH), 1640 (Ar), 1590, 1580 (Py).

P.M.R. δ(d^6DMSO) ppm, 12.36 (1H, brs, NH), 8.55 (1H, d, J=2H_z, H-2'), 8.36, 8.30 (1H, dd, J=2H_z, J=6H_z, H-6'), 7.6 (1H, m, H-4'), 7.75-7.33 (5H, m), 4.35 (1H, q, J=8H_z, CH-CH_3), 1.66 (3H, d, J=8H_z, CH_3-CH).

^{13}C.M.R. δ(d^6DMSO) ppm, C-2, 123.2; C-3, 119.7; C-3a, 123.2; C-4, 114.9; C-5, 118.6; C-6, 105.8; C-7, 148.0; C-7a, 142.1; C-8, 33.8; C-9, 21.8; C-1', 148.8; C-3', 147.1; C-4', 123.2; C-5', 134.4; C-6', 130.5. [Found: C, 75.1; H, 5.4; N, 11.4; $C_{15}H_{13}N_2F$ requires: C, 75.0; H, 5.45; N, 11.7%].

3-[1-(3'-Pyridyl)ethyl]-7-chloroindole (139, R=7-Cl)

m.p. 156-7°.

M.S. m/e M^+ 256.

U.V. λ_{max} (ε) n.m., 221 (56,200), 270 (13,700), 285 (12,050), 296 (9,760).

I.R. ν_{max} cm^{-1}, 3420, 3140 (NH), 1620 (Ar), 1590, 1580 (Py).

P.M.R. δ(d^6DMSO) ppm, 11.24 (1H, brs, NH), 8.60 (1H, d, J=$2H_z$, H-2'), 8.40, 8.37 (1H, dd, J=$2H_z$, J=$6H_z$, H-6'), 7.65 (1H, m, H-4'), 7.4-6.8 (5H, m), 4.40 (1H, q, J=$8H_z$, CH-CH_3), 1.7 (3H, d, H=$8H_z$, CH_3-CH).

^{13}C.M.R. δ(d^6DMSO) ppm, C-2, 123.3; C-3, 119.9; C-3a, 115.9; C-4, 119.3; C-5, 120.5; C-6, 117.7; C-7, 133.3; C-7a, 141.9; C-8, 33.7; C-9, 21.7; C-1', 148.7; C-3', 147.0; C-4', 120.5; C-5', 134.4; C-6', 128.1. [Found: C, 71.0; H, 5.0; N, 11.0; $C_{15}H_{13}N_2Cl$ requires: C, 70.2; H, 5.1; N, 10.9%].

3-[1-(3'-Pyridyl)ethyl]-7-methylindole (139, R=7-Me)

m.p. 168-9°.

M.S. m/e M^+ 236.

U.V. λ_{max} (ε) n.m., 219 (47,290), 260 (16,290), 266 (16,110), 280 (1,383), 290 (1,097), 341 (406).

I.R.(P) ν_{max} cm^{-1}, 3410, 3120 (NH), 1615 (Ar), 1590, 1580 (Py).

P.M.R. δ(d^6DMSO) ppm, 10.82 (1H, brs, NH), 8.52 (1H, d, J=$2H_z$, H-2'), 8.36, 8.28 (1H, dd, J=$2H_z$, J=$6H_z$, H-6'), 7.6 (1H, m, H-4'), 7.28-6.73 (5H, m), 4.36 (1H, q, J=$8H_z$, CH-CH_3), 2.45 (3H, s, CH_3-Ar), 1.68 (3H, d, J=$8H_z$, CH_3-CH).

^{13}C.M.R. δ(d^6DMSO) ppm, C-2, 123.2; C-3, 119.0; C-3a, 121.5; C-4, 118.5; C-5, 121.5; C-6, 116.3; C-7, 125.9; C-7a, 142.4; C-8, 33.9; C-9, 21.9; C-1', 148.8; C-3', 147.0; C-4', 121.5; C-5', 134.4; C-6', 136.1; Me, 16.6. [Found: C, 81.0; H, 6.5; N, 12.0; $C_{16}H_{16}N_2$ requires: C, 81.35; H, 6.8; N, 11.9%].

1-Acetyl-3-{1-[3'-(4'-cyanopyridyl)]ethyl}-5-methoxyindole (54a, R=5-MeO)

The pyridylethylindole (1.5 g), acetic anhydride (20 cm^3) and triethylamine (0.2 g) were heated at reflux for thirty minutes,

evaporated, cooled and poured on to crushed ice (100 g). The resulting solution was cautiously basified and extracted with dichloromethane (3 x 100 cm^3), dried and evaporated to give a pale amber oil which solidified on standing. Re-crystallised from methanol (750 mg).

A solution of O-mesitylenesulphonylhydroxylamine (0.55 g, 1 mol.eq.) in dichloromethane (5 cm^3) was added to a stirred cooled (0°) solution of the acetyl derivative (750 mg) in dichloromethane (15 cm^3) and stirred in the cold for thirty minutes. Next the reaction mixture was poured into dry ether (250 cm^3), whereupon a white solid formed. This was dissolved in water (25 cm^3) and treated with acetic anhydride (25 cm^3) and stirred in the cold for thirty minutes. Then it was basified and extracted with dichloromethane (5 x 100 cm^3), dried and evaporated to give a purple coloured oil. This was dissolved in acetone (50 cm^3) and iodomethane (25 cm^3) and heated at reflux for forty five minutes. On cooling a yellow amorphous solid formed (1.5 g).

The yellow salt was dissolved in water (25 cm^3) containing ammonium chloride (0.65 g), and treated with a potassium cyanide solution (3 mol.eq.) in water (10 cm^3) and stirred for an hour. Next it was extracted with dichloromethane (5 x 100 cm^3), washed with water (3 x 25 cm^3), dried and evaporated to give an amber oil. This oil was dissolved in ethanol (50 cm^3) and irradiated with soft U.V. light for an hour.

The solvent evaporated, the oil was chromatographed on silica with ether eluant. Concentration of the eluants afforded an off white solid which re-crystallised from methanol (426 mg).

m.p. 95-96°.

P.M.R. δ(d^6DMSO) ppm, 8.65 (1H, s, H-2'), 8.62 (1H, d, $\underline{J}$=6H_z, H-6'), 8.3 (1H, d, $\underline{J}$=10H_z, H-7), 7.5 (1H, d, $\underline{J}$=6H_z, H-5'), 7.41 (1H, s, H-2), 6.96, 6.86 (1H, dd, $\underline{J}$=2H_z, $\underline{J}$=10H_z, H-6), 6.64 (1H, d, $\underline{J}$=2H_z, H-4), 4.64 (1H, q, $\underline{J}$=8H_z, $\underline{CH}$-CH_3), 3.75 (3H, s, $\underline{CH_3}$-O), 2.65 (3H, s, $\underline{CH_3}$-CO), 1.85 (3H, d, $\underline{J}$=8H_z, $\underline{CH_3}$-CH). [Found: C, 71.3; H, 5.4; N, 13.0; $C_{19}H_{17}N_3O_2$ requires: C, 71.45; H, 5.4; N, 13.12%].

9-Methoxy ellipticine

A solution of the nitrile (426 mg, 1 mol.eq.) in dry tetrahydrofuran (5 cm^3) was added dropwise to a cooled (-78°) stirred solution of methyllithium (1.4 M, 4 cm^3, 4 mol.eq.) in dry tetrahydrofuran (10 cm^3) under an atmosphere of nitrogen and stirred for thirty minutes in the cold before allowing to warm to room temperature over an hour. The resulting red solution was poured on to ice cold 20% acetic acid (50 cm^3) and warmed on a steam bath for an hour. Then the reaction mixture was cautiously basified and extracted with dichloromethane (15 x 75 cm^3), dried and evaporated to give a yellow solid.

Re-crystallised from methanol (0.35 g, 94%).

m.p. 268° (lit.[49] 270°).

M.S. m/e (int. %), M^+ 276 (100), 261 (71), 233 (17).

U.V. λ_{max} (ε) n.m., 245 (21,380), 276 (36,176), 292 (42,640), 305 (26,190), 336 (5,280), 353 (2,876).

I.R.(P) ν_{max} cm^{-1}, 3440, 3150 ($\underline{NH}$), 1620 (Ar), 1598 (Py).

P.M.R. δ(d^6DMSO) ppm, 11.89 (1H, brs, NH), 9.68 (1H, brs, H-1), 8.42 (1H, brd, $\underline{J}$=6H_z, H-3), 7.85 (1H, brd, $\underline{J}$=6H_z, H-4), 7.84 (1H, brd, $\underline{J}$=2H_z, H-10), 7.50 (1H, d, $\underline{J}$=10H_z, H-7), 7.25, 7.16 (1H, dd,

$\underline{J}$=2H_z, $\underline{J}$=10H_z, H-8), 3.91 (3H, s, $\underline{CH_3}$-O), 3.2 (3H, s, 11-$\underline{CH_3}$), 2.75 (3H, s, 5-$\underline{CH_3}$).

^{13}C.M.R. δ(d^6DMSO) ppm, C-1, 149.6; C-3, 140.3; C-4, 123.6; C-4a, 132.4; C-5, 111.1; C-5a, 141.3; C-6a, 137.4; C-7, 107.8; C-8, 108.0; C-9, 153.2; C-10, 115.1; C-10a, 121.7; C-10b, 123.4; C-11, 128.1; C-11a, 126.2; C-12, 14.1; C-13, 11.6; MeO, 55.9. [Found: C, 78.0; H, 5.8; N, 10.2; calculated for $C_{18}H_{16}N_2O$ C, 78.3; H, 5.8; N, 10.1%].

The I.R., P.M.R., U.V. and the melt of the natural product are superimposable with the corresponding spectra of the synthetic material.

Following the same procedure 7-fluoro, chloro and methyl ellipticine were synthesised.

7-Fluoroellipticine

m.p. 245° dec.

M.S. m/e (int.%), $M^{\ddagger}$ 264 (100), 249 (20), 132 (11).

U.V. λ_{max} (ε) n.m., 242 (28,490), 276 (42,110), 284 (59,050), 300 (39,200), 353 (4,030).

I.R.(P) ν_{max} cm^{-1}, 3420, 3110 (NH), 1640 (Ar), 1600, 1580 (Py), 1390 (CF).

P.M.R. δ(d^6DMSO) ppm, 12.61 (1H, brs, NH), 9.65 (1H, s, H-1), 8.28 (1H, d, $\underline{J}$=6H_z, H-3), 8.10 (1H, d, $\underline{J}$=6H_z, H-4), 7.85 (1H, brd, $\underline{J}$=8H_z, H-10), 7.4-7.0 (2H, m, H-9&8), 2.96 (3H, s, 11-$\underline{CH_3}$), 2.60 (3H, s, 5-$\underline{CH_3}$).

^{13}C.M.R. δ(d^6DMSO) ppm, C-1, 144.1; C-3, 143.9; C-4, 121.0; C-4a, 134.0; C-5, 111.0; C-5a, 142.7; C-6a, 130.3; C-7, 149.4; C-8, 113.8; C-9, 125.6; C-10, 119.6; C-10a, 120.9; C-10b, 121.0; C-11, 127.9; C-11a, 133.3; C-12, 14.6; C-13, 11.8. [Found: C, 77.4;

H, 5.0; N, 10.5; $C_{17}H_{13}N_2F$ requires C, 77.25; H, 5.0; N, 10.6%].

7-Chloroellipticine

m.p. 315-320°.

M.S. m/e (int.%) M^+ 280 (100), 265 (20), 140 (12).

U.V. λ_{max} (ε) n.m., 238 (29,340), 266 (40,040), 276 (62,660), 286 (69,200), 330 (6,120), 345 (4,850), 378 (4,810).

I.R.(P) ν_{max} cm^{-1}, 3150, 3100 (NH), 1618 (Ar), 1600, 1570 (Py).

P.M.R. δ(d^6DMSO/CF_3CO_2D) ppm, 9.66 (1H, s, H-1), 8.32 (1H, d, $\underline{J}$=6H_z, H-3), 8.08 (1H, d, $\underline{J}$=6H_z, H-4), 7.92 (1H, d, $\underline{J}$=8H_z, H-10), 7.40 (1H, d, $\underline{J}$=8H_z, H-8), 7.12, 7.05 (1H, dd, $\underline{J}_1$=$\underline{J}_2$=10H_z, H-9), 2.92 (3H, s, 11-$\underline{CH_3}$), 2.60 (3H, s, 5-CH_3).

^{13}C.M.R. δ(d^6DMSO/CH_3CO_2D) ppm, C-1, 143.7; C-3, 143.7; C-4, 122.5; C-4a, 134.6; C-5, 111.4; C-5a, 141.1; C-6a, 138.9; C-7, 133.4; C-8, 115.7; C-9, 124.0; C-10, 119.7; C-10a, 120.5; C-10b, 124.0; C-11, 127.9; C-11a, 139.5; C-12, 14.7; C-13, 12.1 [Found: C, 73.0; H, 4.7; N, 9.8; $C_{17}H_{13}N_2Cl$ requires C, 72.7; H, 4.7; N, 10.0%].

7-Methylellipticine

m.p. 298-300°.

M.S. m/e (int.%), M^+ 260 (100), 245 (27).

U.V. λ_{max} (ε) n.m., 239 (28,410), 280 (58,410), 287 (63,600), 332 (5,090).

I.R.(P) ν_{max} cm^{-1}, 3450, 3200 (NH), 1620 (Ar), 1590 (Py).

P.M.R. δ(d^6DMSO/CF_3CO_2D) ppm, 9.58 (1H, s, H-1), 8.25 (1H, d, $\underline{J}$=6H_z, H-3), 8.06 (1H, d, $\underline{J}$=6H_z, H-4), 7.88 (1H, d, $\underline{J}$=8H_z, H-10), 7.3-7.03 (2H, m, H-8&9), 2.90 (3H, s, 11-CH_3), 2.60 (3H, s, 5-CH_3), 2.48 (3H, s, $\underline{CH_3}$-Ar).

^{13}C.M.R. δ(d^6DMSO/CF_3CO_2D) ppm, C-1, 144.2; C-3, 143.1; C-4, 119.4; C-4a, 129.4; C-5, 110.5; C-5a, 141.5; C-6a, 132.7; C-7, 126.0;

C-8, 120.8; C-9, 121.8; C-10, 121.1; C-10a, 119.8; C-10b, 121.9; C-11, 127.3; C-11a, 133.8; C-12, 14.7; C-13, 12.1; Me, 17.3. [Found: C, 83.1; H, 6.2; N, 10.8; $C_{18}H_{16}N_2$ requires: C, 83.1; H, 6.2; N, 10.8%].

3'(2-Methyl-1,3-dioxlan-2-yl)pyridine (150)

3-Acetylpyridine (20 g, 1 mol.eq.), ethylene glycol (50 g, 5 mol.eq.) and 4-toluenesulphonic acid (38 g, 1.2 mol.eq.) were refluxed in dry benzene (200 cm^3) using a Dean-Stark apparatus for six hours.

The resulting mixture was poured into 50% sodium carbonate solution (500 cm^3) and extracted with dichloromethane (5 x 100 cm^3), dried and evaporated to give a colourless oil (25 g, 89%). P.M.R. $\delta(CDCl_3)$ ppm, 8.76 (1H, d, $J=2H_z$, H-2), 8.60, 8.55 (1H, dd, $J=2H_z$, $J=6H_z$, H-6), 7.8 (1H, m, H-4), 7.25, 7.18 (1H, dd, $J_1=J_2=6H_z$, H-5), 3.88 (4H, comp sym, d, OCH_2CH_2O), 1.60 (3H, s, CH_3-).

1-Methylacetimido-3'-(2-methyl-1,3-dioxolan-2-yl)pyridinium iodidide (151)

A cooled solution of O-mesitylenesulphonylhydroxylamine (8.9 g, 1 mol.eq.) in dichloromethane (20 cm^3) was added dropwise to a cooled, stirred solution of the pyridine (6.8 g, 1 mol.eq.) in dichloromethane (10 cm^3) and stirred for a further thirty minutes in the cold. The reaction mixture was then poured into dry ether (500 cm^3) whereupon a white solid formed. The ether was decanted and the solid dissolved in iced water (40 cm^3). The aqueous solution of the salt was treated with acetic anhydride (35 cm^3) and stirred in the cold for thirty minutes, basified and extracted with dichloromethane (3 x 100 cm^3). The combined

extracts were dried and evaporated. The ensuing amber oil was dissolved in acetone (25 cm^3), treated with iodomethane (25 cm^3) and heated at reflux for forty five minutes. On cooling a bright yellow solid formed.

P.M.R. $\delta(d^6DMSO)$, 9.35 (2H, m, H-2&6), 8.75 (1H, m, H-4), 8.45 (1H, m, H-5), 3.97 (4H, comp.sym., d, $-OCH_2CH_2O-$), 3.73 (3H, s, $N-\underline{CH_3}$), 3.30 (3H, s, $N-CO\underline{CH_3}$), 1.70 (3H, s, CH_3).

3'-(2-Methyl-1,3-dioxolan-2-yl)-6'-ethylpyridine (152a)

The pyridine methiodide (20 g, 1 mol.eq.) was added portionwise to a cooled stirred solution of ethylmagnesium bromide (3 mol.eq.) in dry tetrahydrofuran (75 cm^3) controlling the ensuing exothermic reaction. Once the initial exothermic reaction subsided, the mixture was refluxed for twenty hours, cooled and evaporated to give a viscous oil. This oil was well shaken with water (15 cm^3) and extracted with dichloromethane (3 x 100 cm^3), dried and evaporated to give a red oil, which was dissolved in ethanol (100 cm^3) and irradiated with soft U.V. light for five hours. On evaporation it gave a viscous oil, which was chromatographed on basic alumina with diethyl ether as the eluant to afford a pale yellow oil (4.8 g, 45%).

U.V. λ_{max} n.m., 217, 262, 267, 274.

I.R.(L) ν_{max} cm^{-1}, 1600 (Py).

P.M.R. $\delta(CDCl_3)$ ppm, 8.62 (1H, d, $\underline{J}=2H_z$, H-2), 7.72, 7.64 (1H, dd, $\underline{J}=2H_z$, $\underline{J}=8H_z$, H-4), 7.12 (1H, d, $\underline{J}=8H_z$, H-5), 3.9 (4H, comp.sym., d, $-O\underline{CH_2}\underline{CH_2}O-$), 2.84 (2H, q, $\underline{J}=8H_z$, $\underline{CH_2}-CH_3$), 1.62 (3H, s, CH_3-C), 1.25 (3H, t, $\underline{J}=8H_z$, $\underline{CH_3}-CH_2$).

Condensation of (152a) with indole (153)

Indole (1.8 g, 1 mol.eq.) and ethyl pyridine (3 g, 1 mol.eq.)

were heated at reflux in ethanolic hydrochloric acid for three hours. The resulting red solution was evaporated, dissolved in iced water (50 cm^3), filtered and basified to give a pale pink solid.

Attempts to re-crystallise failed, therefore vacuum sublimed to afford a colourless solid.

m.p. 112°.

M.S. m/e $M^{\cdot+}$ 250.

U.V. λ_{max} n.m., 223, 263, 295.

I.R.(P) ν_{max} cm^{-1}, 3260, 3100 (NH), 1600 (Ar).

P.M.R. $\delta(d^6$DMSO) ppm, 10.92 (1H, s, NH), 8.45 (1H, d, $\underline{J}=2H_z$, H-2'), 7.54, 7.46 (1H, dd, $\underline{J}=2H_z$, $\underline{J}=8H_z$, H-4'), 7.4-6.8 (6H, m), 4.32 (1H, q, $\underline{J}=8H_z$, $\underline{CH}-CH_3$), 2.38 (2H, q, $\underline{J}=8H_z$, CH_2CH_3), 1.64 (3H, d, $\underline{J}=8H_z$, $\underline{CH_3}-CH$), 1.13 (3H, t, $\underline{J}=8H_z$, $\underline{CH_3}-CH_2$).

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PUBLICATIONS

1. An efficient synthesis of 3-[1-(3-pyridyl)ethyl]indoles.
   M. Sainsbury and D.K. Weerasinghe, J.C.S. Chem. Comm., 1981, 630.
2. Chemistry of 6H-pyrido[4,3-b]carbazoles, part 9.
   M. Sainsbury, D. Dolman, D. Watkins and D.K. Weerasinghe, J.C.S. Perkin I, in the press.
3. Chemistry of 6H-pyrido[4,3-b]carbazoles, part 10.
   M. Sainsbury, D. Watkins and D.K. Weerasinghe, J. Org. Mag. Res., in the press.

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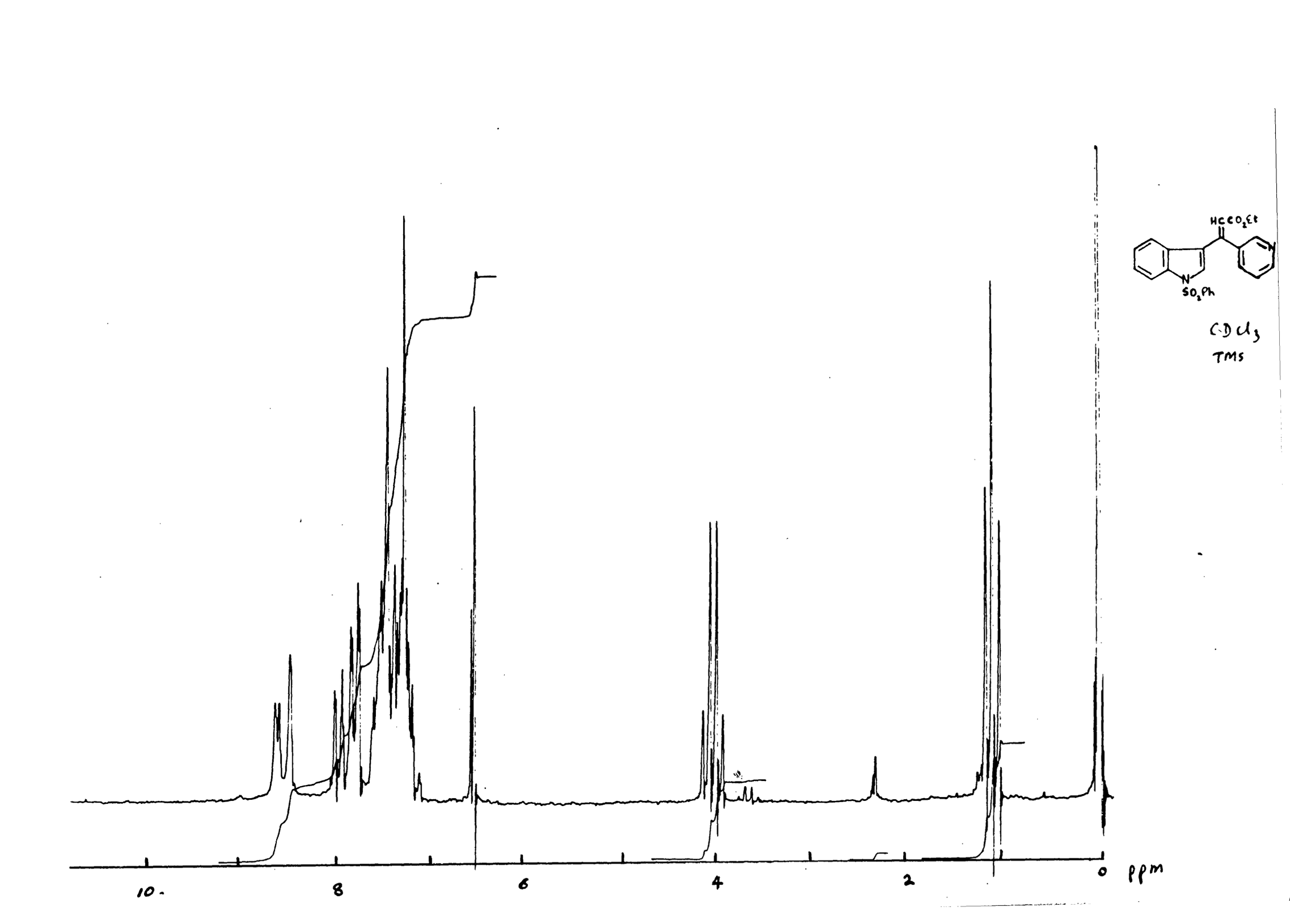
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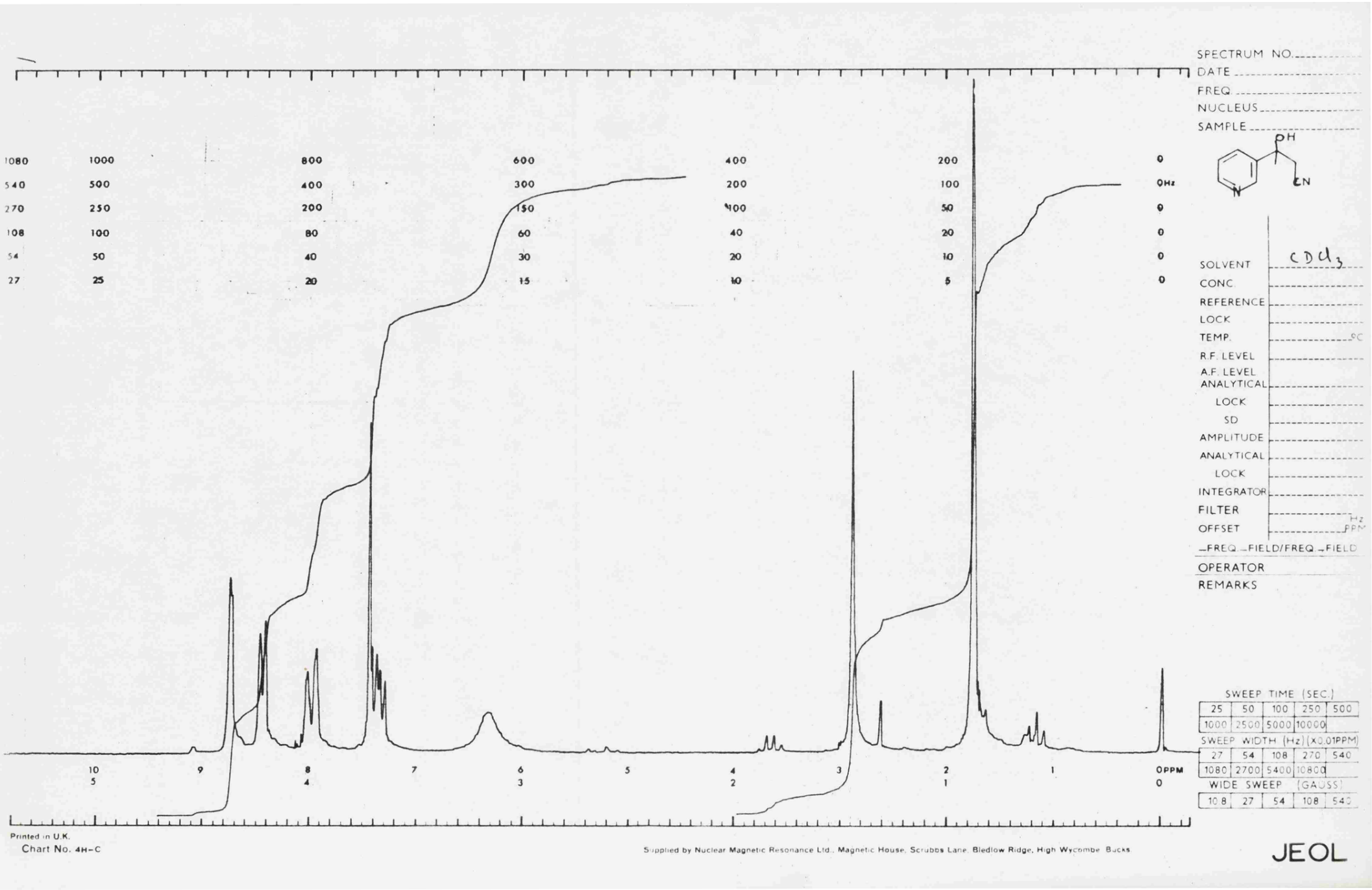

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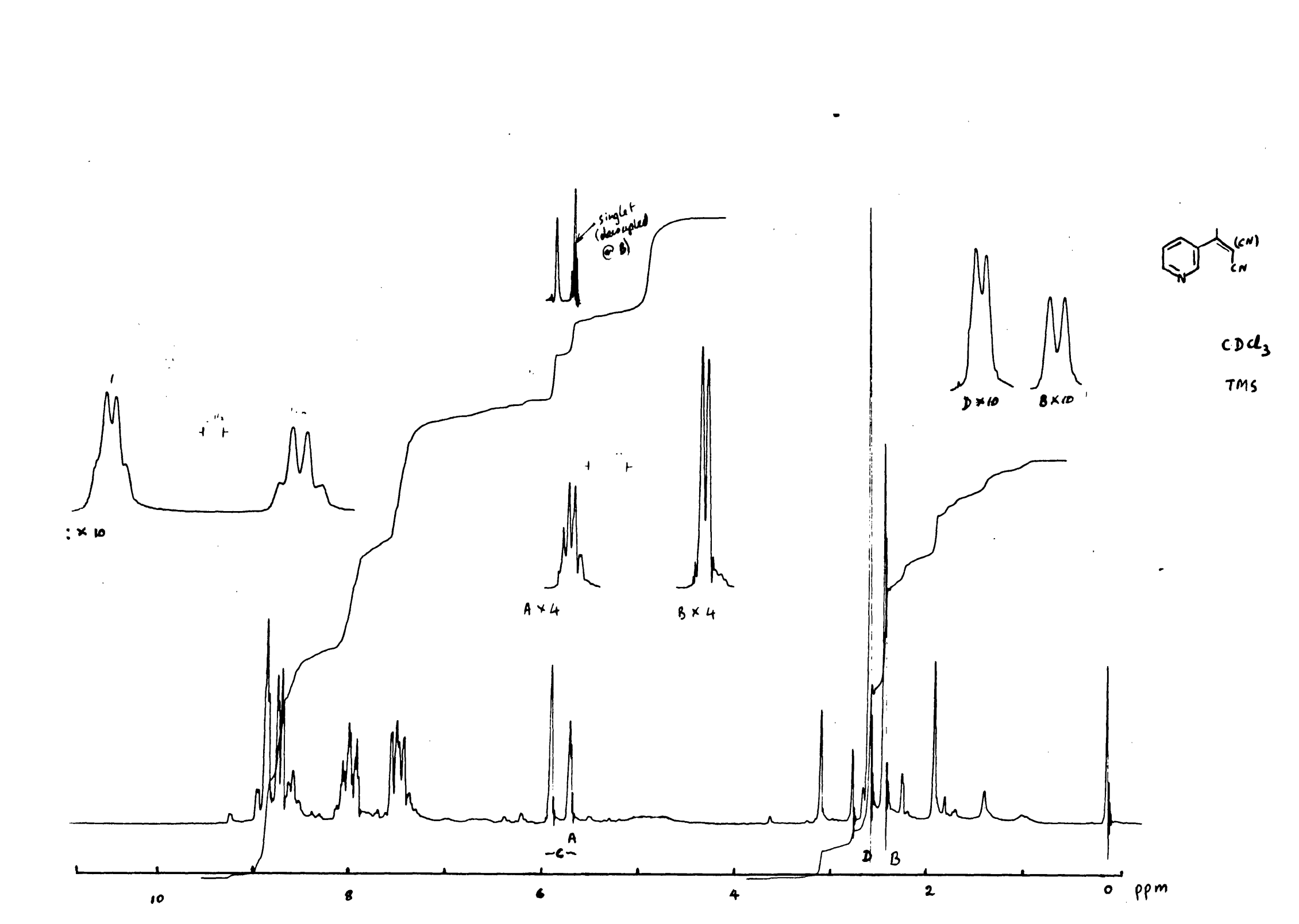
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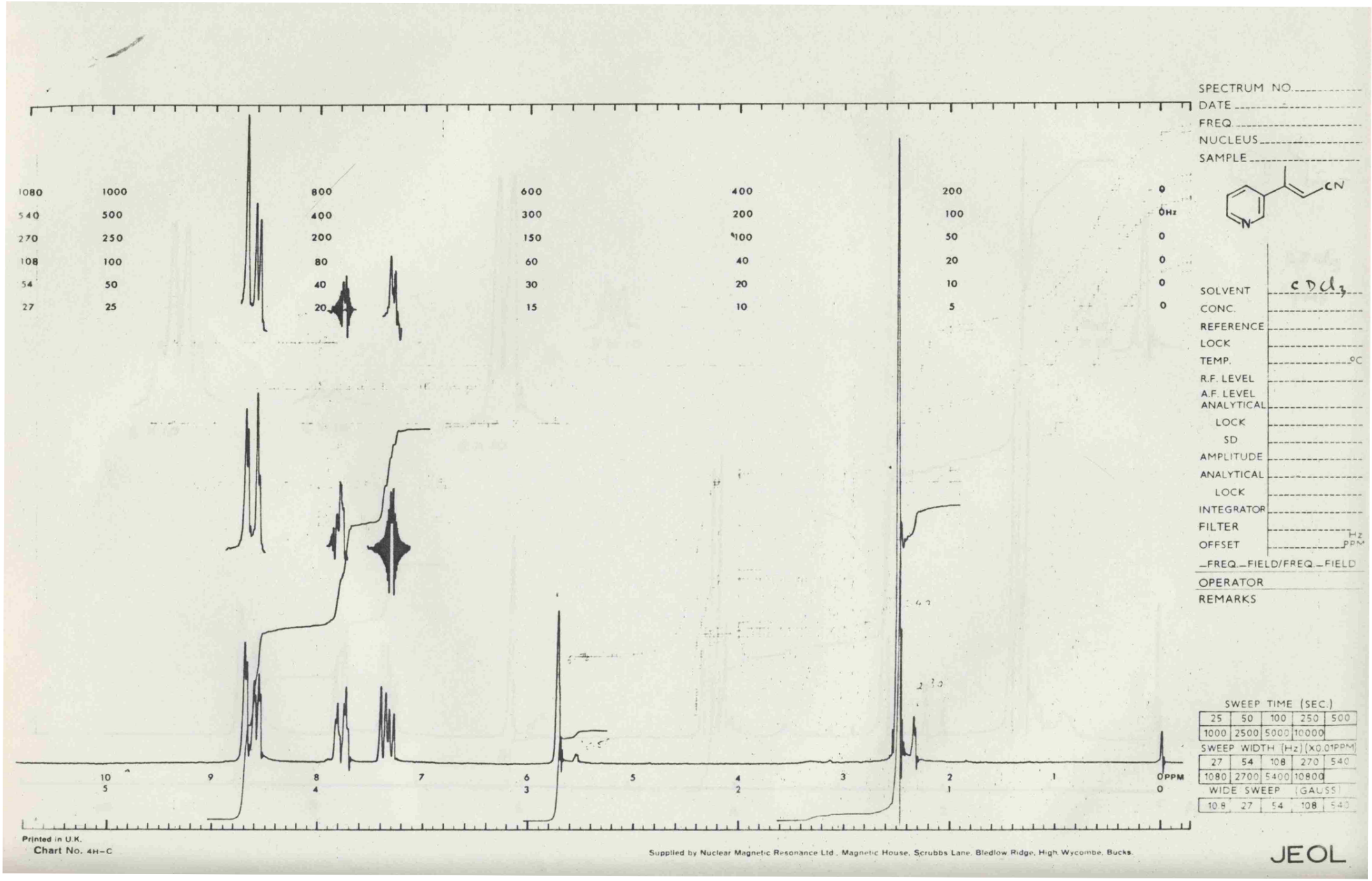

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SOLVENT $CDCl_3$
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A.F. LEVEL
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AMPLITUDE
ANALYTICAL
LOCK
INTEGRATOR
FILTER
OFFSET Hz PPM

FREQ. FIELD/FREQ. FIELD

OPERATOR
REMARKS

SWEEP TIME (SEC.)

25	50	100	250	500
1000	2500	5000	10000	

SWEEP WIDTH (Hz) (X0.01PPM)

27	54	108	270	540
1080	2700	5400	10800	

WIDE SWEEP (GAUSS)

10.8	27	54	108	540

Printed in U.K.
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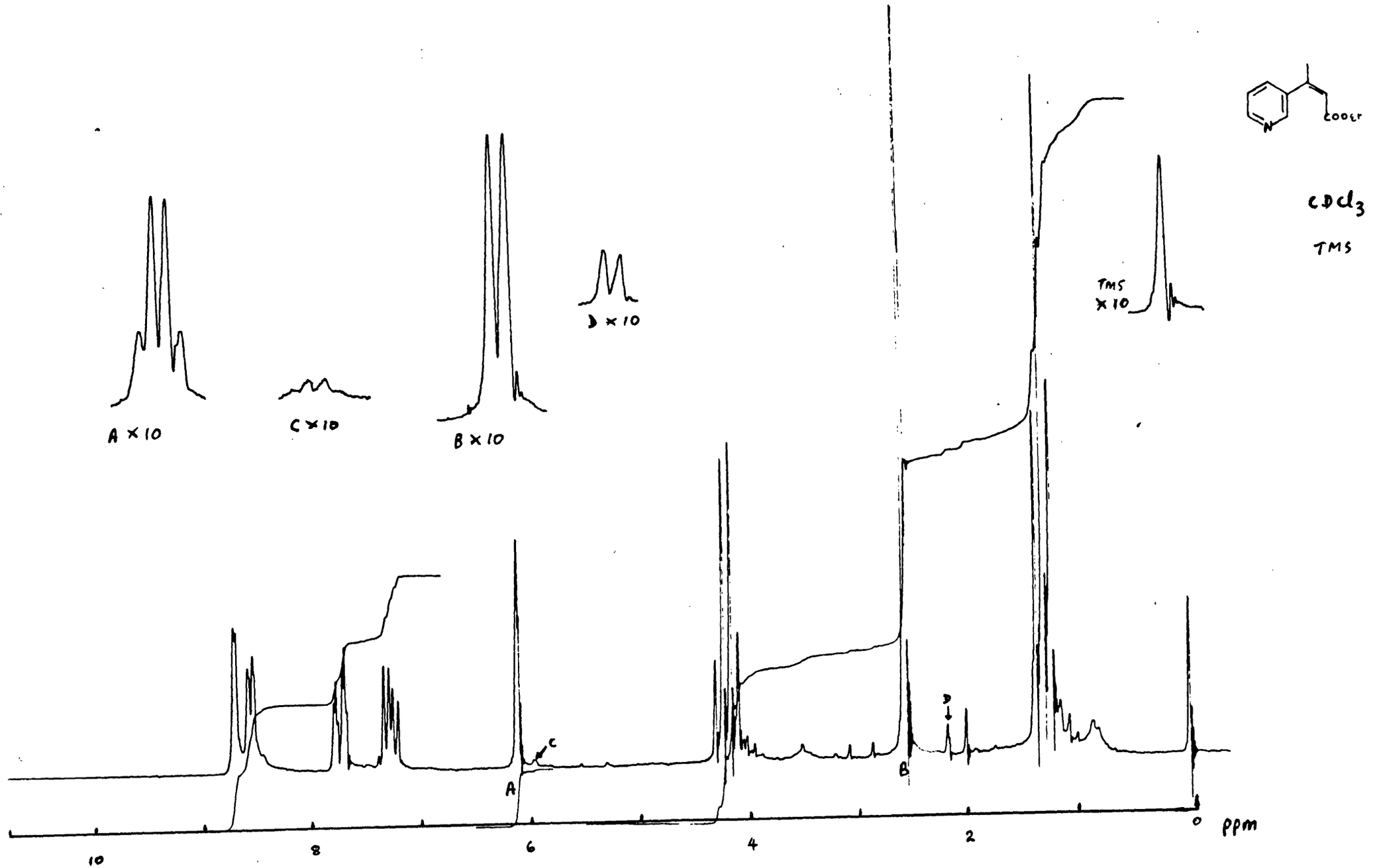
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2000
1800
1600
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1200
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600
400
WAVENUMBER (CM⁻¹)
MeO
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H
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SOLVENT KBr
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CELL PATH
REFERENCE
ORIGIN
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SINGLE B.
T.D. SPEED
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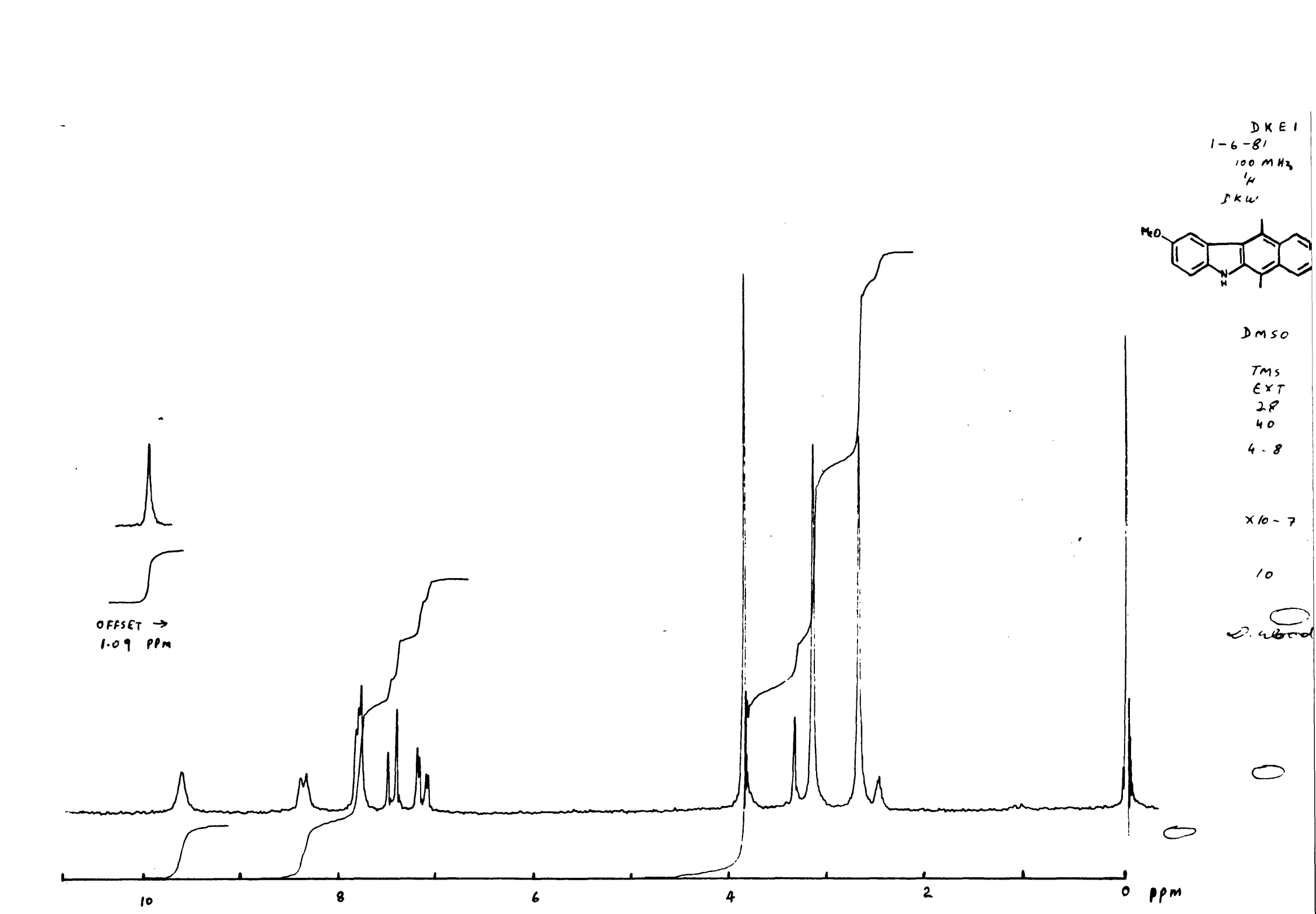
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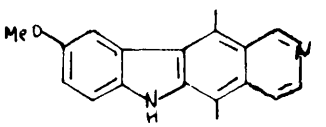

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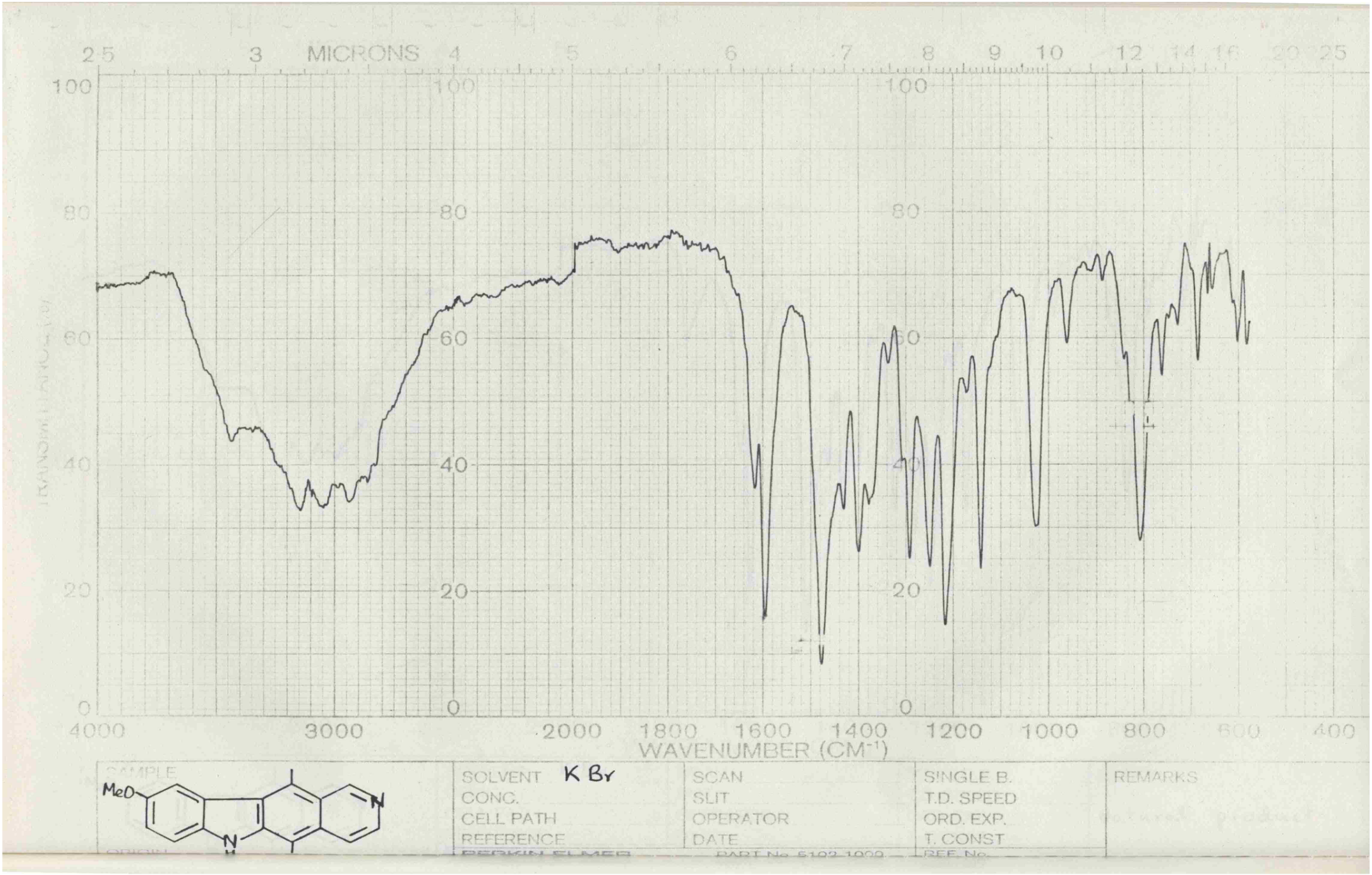
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TRANSMITTANCE (%)
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WAVENUMBER (CM⁻¹)
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SAMPLE
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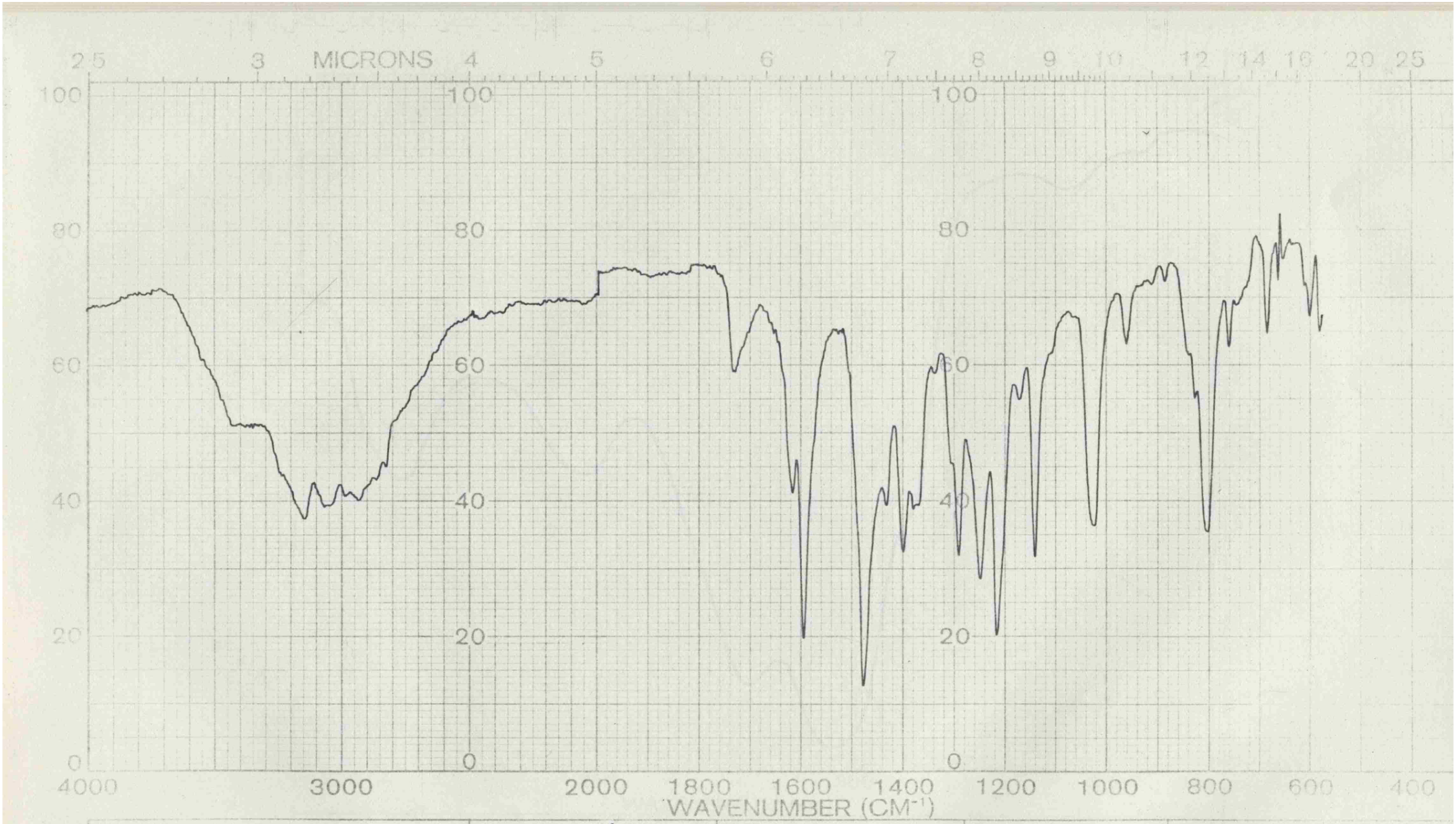
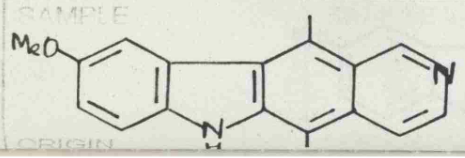


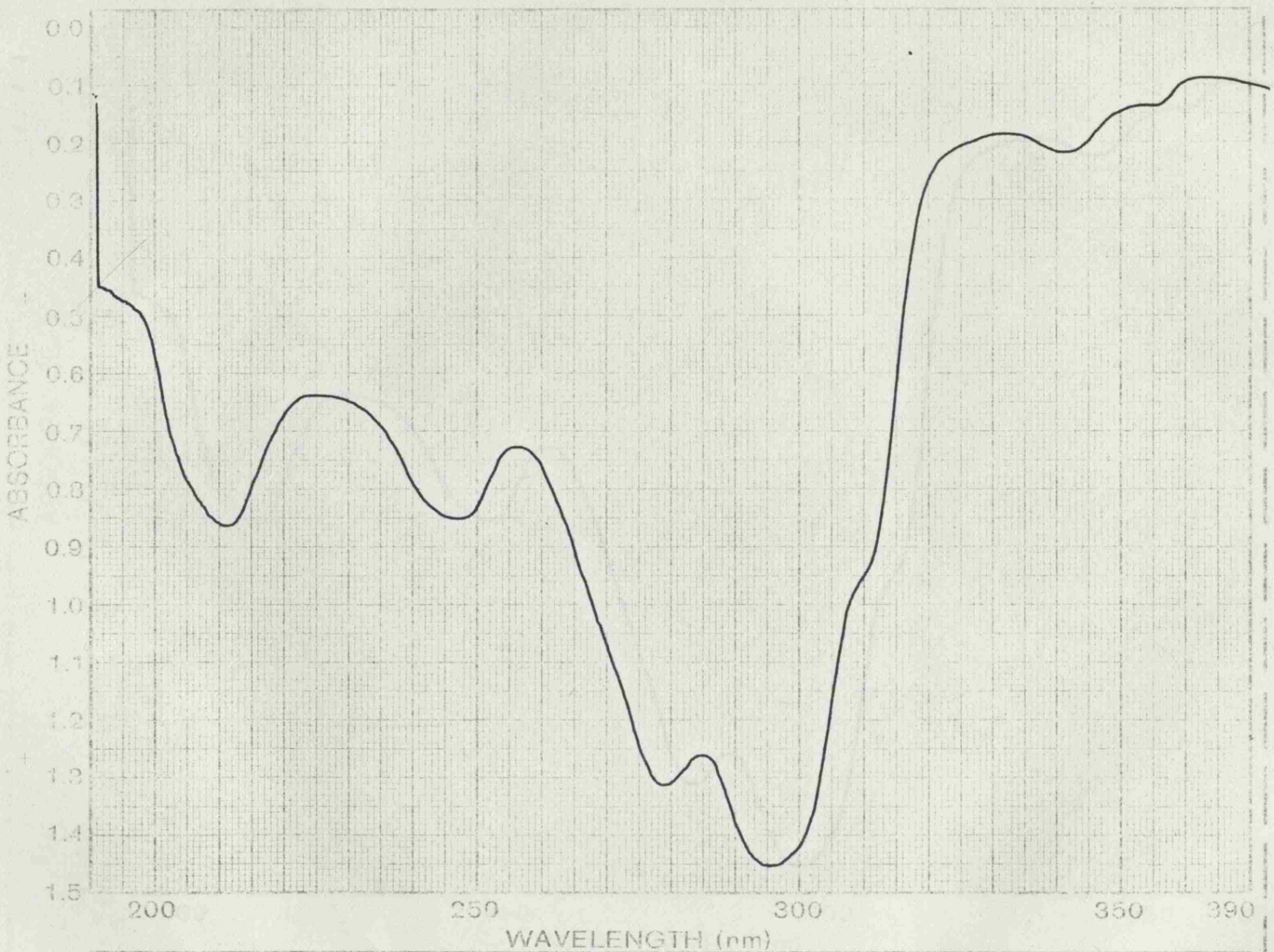
SAMPLE



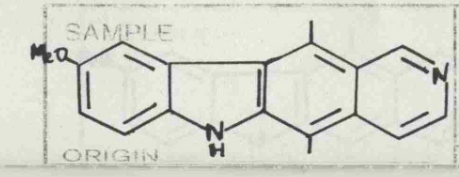
ORIGIN

SOLVENT KBr	SCAN	SINGLE B.	REMARKS
CONC.	SLIT	T.D. SPEED	
CELL PATH	OPERATOR	ORD. EXP.	Natural product
REFERENCE	DATE	T. CONST	

PERKIN-ELMER PART No. 5102-1000 REF No.



SAMPLE



ORIGIN

SOLVENT EtOH
CONC.
CELL PATH
REFERENCE

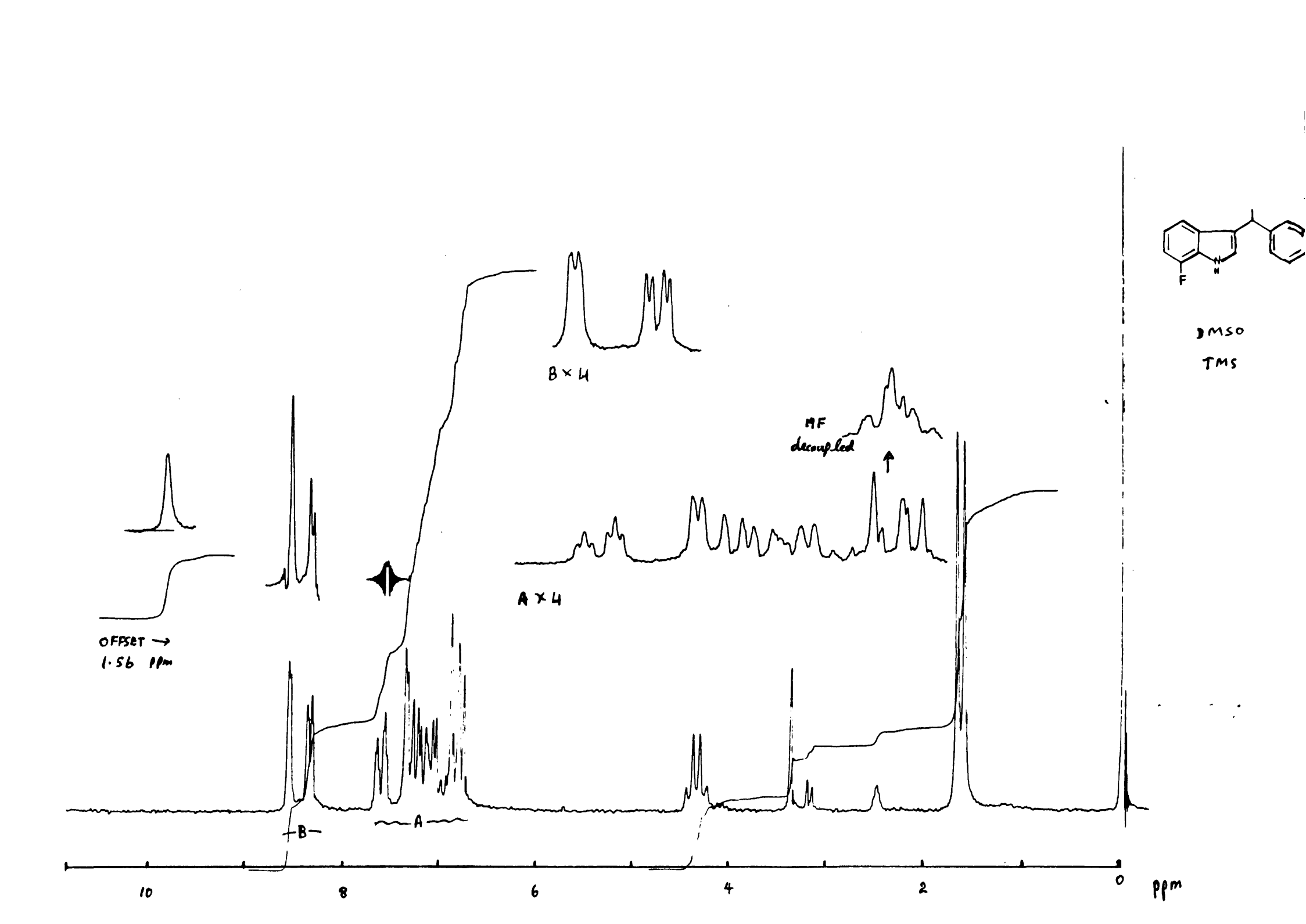
SCAN
SLIT
OPERATOR
DATE

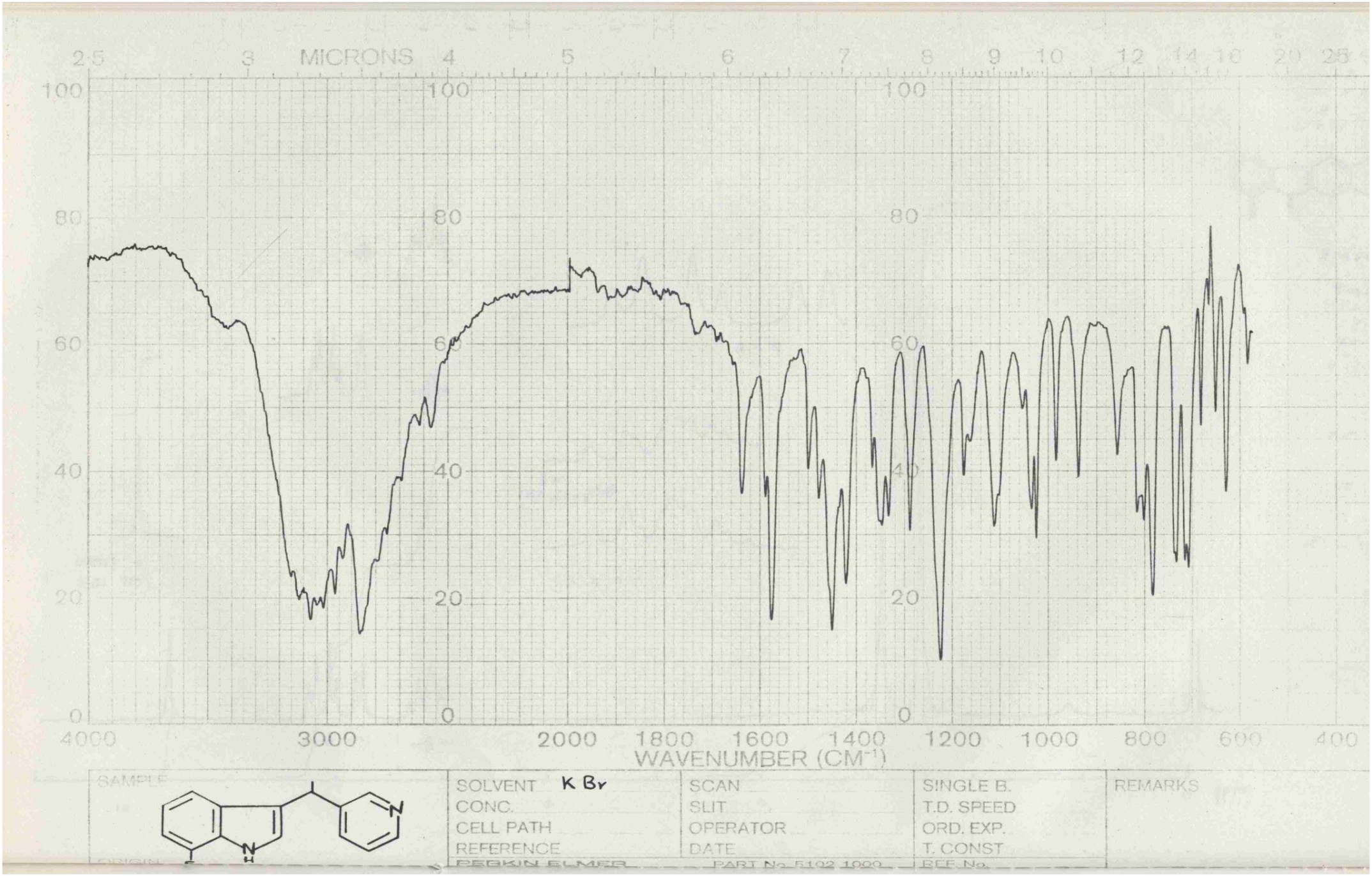
No. 492 5002

REMARKS

REF. No.

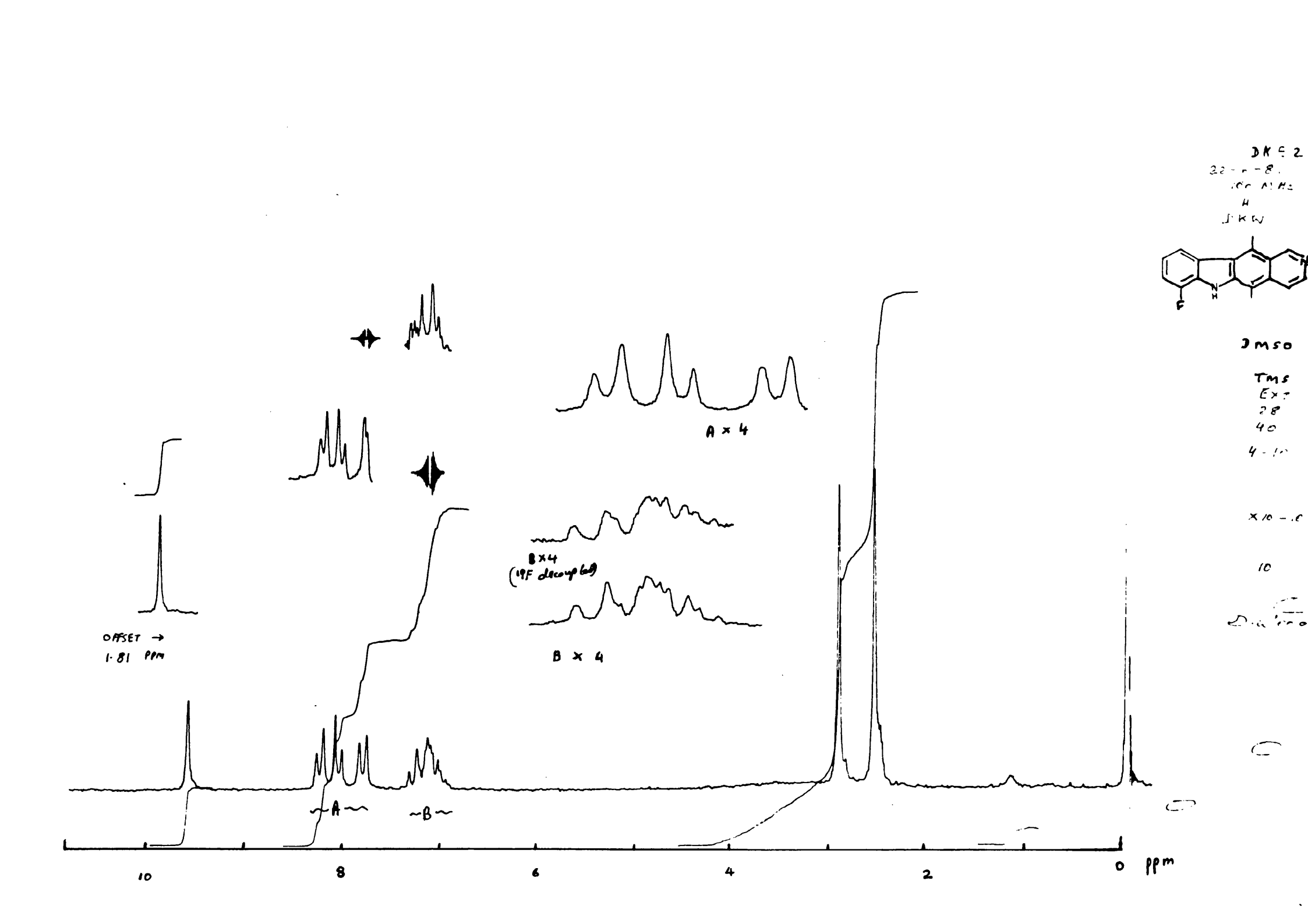

ABSORBANCE
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
200
250
300
350
390
WAVELENGTH (nm)
SAMPLE
MeO
N
N
H
ORIGIN
SOLVENT EtOH
CONC.
CELL PATH
REFERENCE
SCAN
SLIT
OPERATOR
DATE
REMARKS
Natural product
REF. No.


B × 4
MF
decoupled
A × 4
OFFSET →
1·56 ppm
DMSO
TMS
F
N
H
B
A
10
8
6
4
2
0
ppm

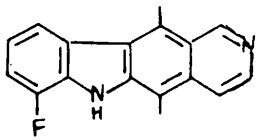


SAMPLE	SOLVENT KBr	SCAN	SINGLE B.
	CONC.	SLIT	T.D. SPEED
	CELL PATH	OPERATOR	ORD. EXP.
	REFERENCE	DATE	T. CONST
ORIGIN	PERKIN ELMER	PART No. 5102 1000	REF. No.

REMARKS


DK 5 2
JMSO
TMS
A x 4
B x 4
(19F decoupled)
B x 4
OFFSET →
1.81 ppm
~A~
~B~
10
8
6
4
2
0
ppm

DKE2



DMSO 5
25mg
TMS
AT

33.45
5.45
4 3.
1.0

8K
0.485
10,000

5000

22

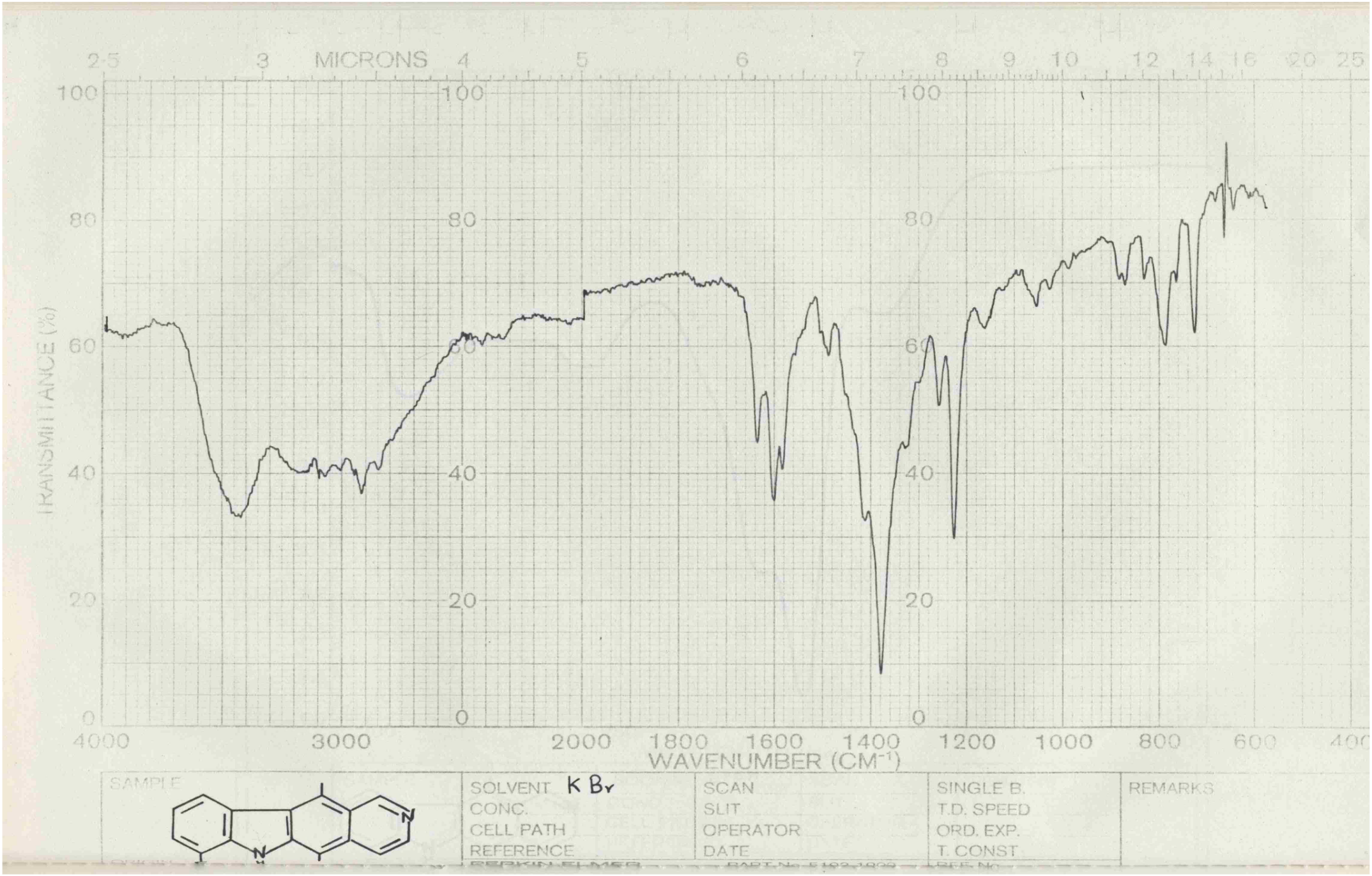
AUTO

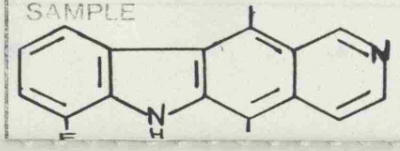
HS

20

23.6.81
Harry

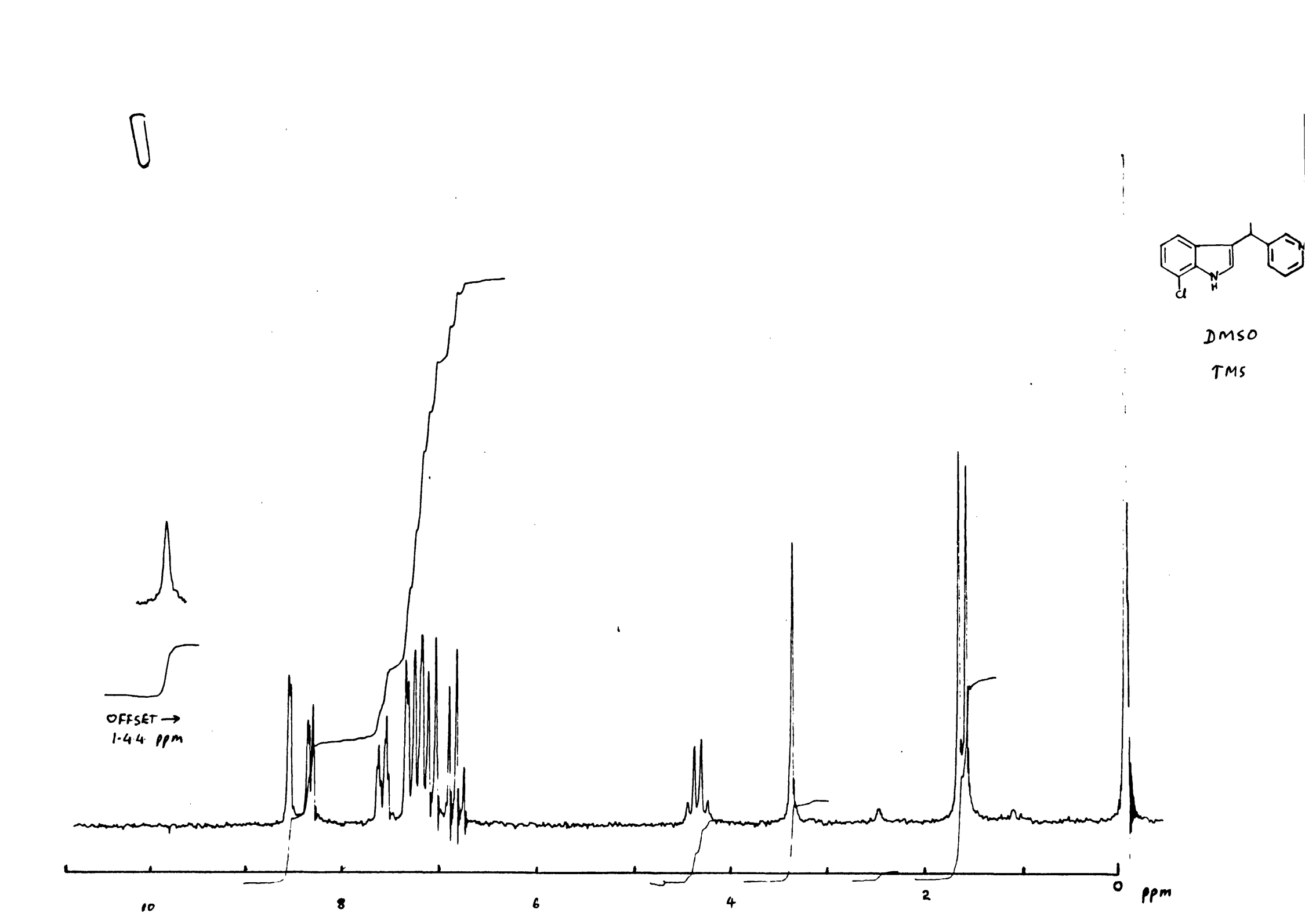
0 ppm

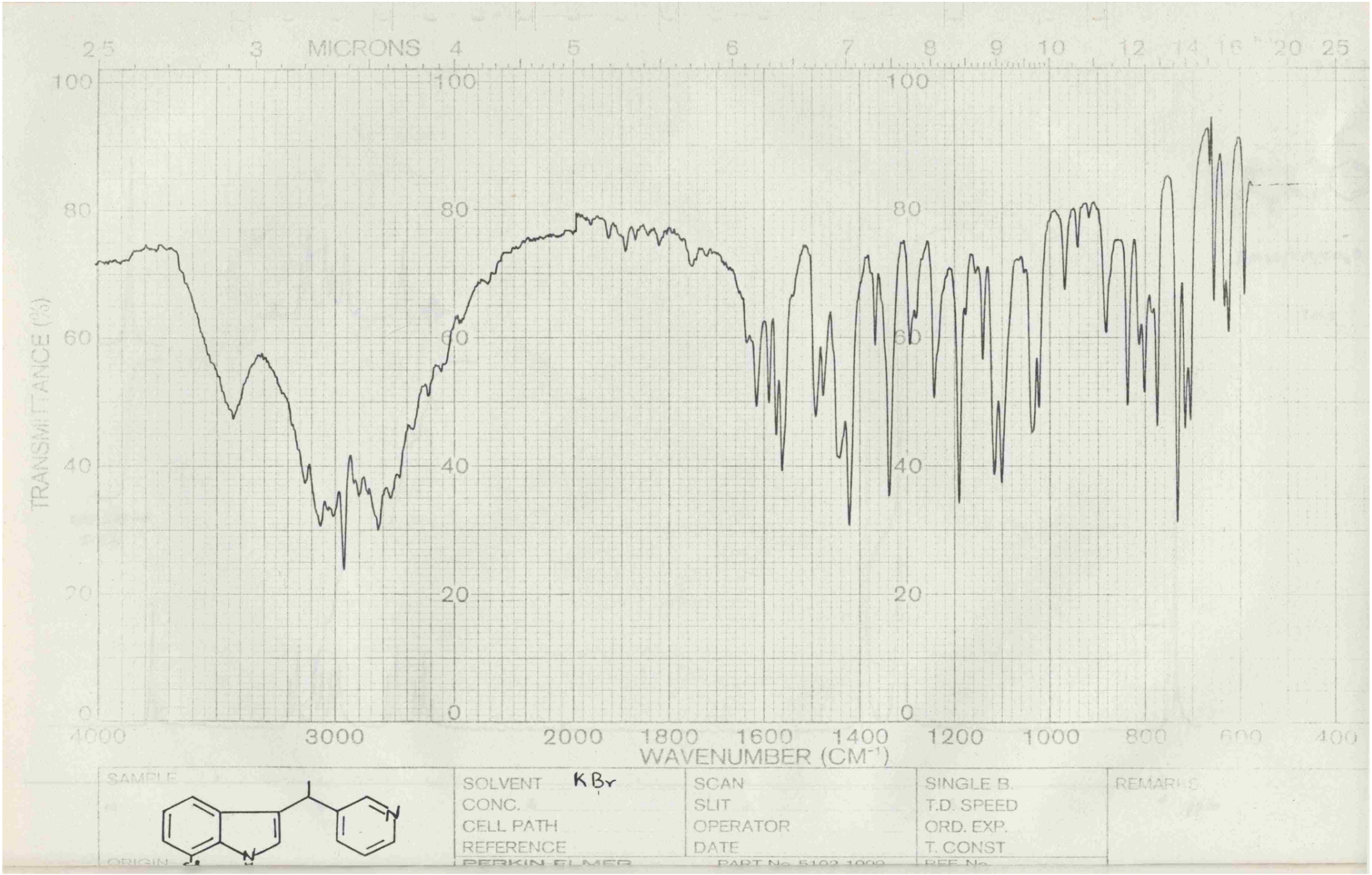

2·5
3
MICRONS
4
5
6
7
8
9
10
12
14
16
20
25
100
80
60
40
20
0
TRANSMITTANCE (%)
4000
3000
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER (CM⁻¹)
SAMPLE
SOLVENT KBr
CONC.
CELL PATH
REFERENCE
SCAN
SLIT
OPERATOR
DATE
SINGLE B.
T.D. SPEED
ORD. EXP.
T. CONST
REMARKS
PERKIN ELMER

SAMPLE 	SOLVENT EtOH	SCAN
	CONC.	SLIT
	CELL PATH	OPERATOR
	REFERENCE	DATE

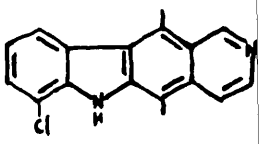
REMARKS

REF. No.


d
N
H
DMSO
TMS
OFFSET →
1·44 ppm
10
8
6
4
2
0
ppm


2.5
3
MICRONS
4
5
6
7
8
9
10
12
14
16
20
25
100
80
60
40
20
0
TRANSMITTANCE (%)
4000
3000
2000
1800
1600
1400
1200
1000
800
600
400
WAVENUMBER (CM⁻¹)
SAMPLE
SOLVENT KBr
CONC.
CELL PATH
REFERENCE
SCAN
SLIT
OPERATOR
DATE
SINGLE B.
T.D. SPEED
ORD. EXP.
T. CONST
REMARKS
ORIGIN
PERKIN ELMER
PART No. 5102-1000
REF. No.

DKE 3



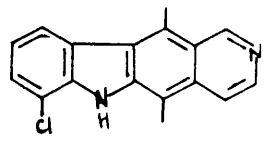
DMSO/CF_3CO_2D

TMS

OFF SET →
5.56

10 8 6 4 2 0 ppm

DK E 3



+TFA

DMSO

5

5

T.M.S

RT

33.45

54.5

4 3 0

1 0

81c

0.485 7

5,000

5,000

2 2

AUTO

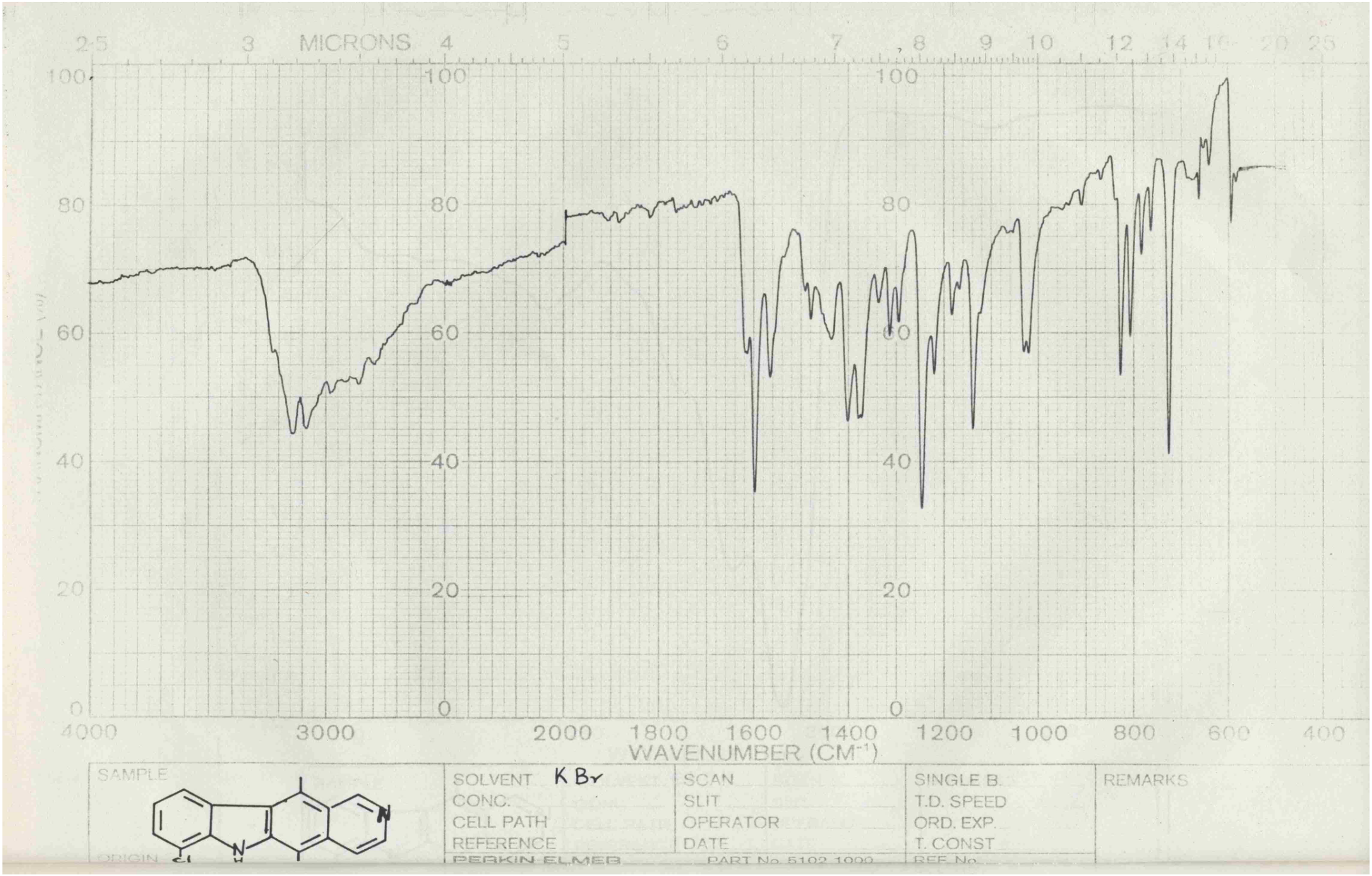
H6

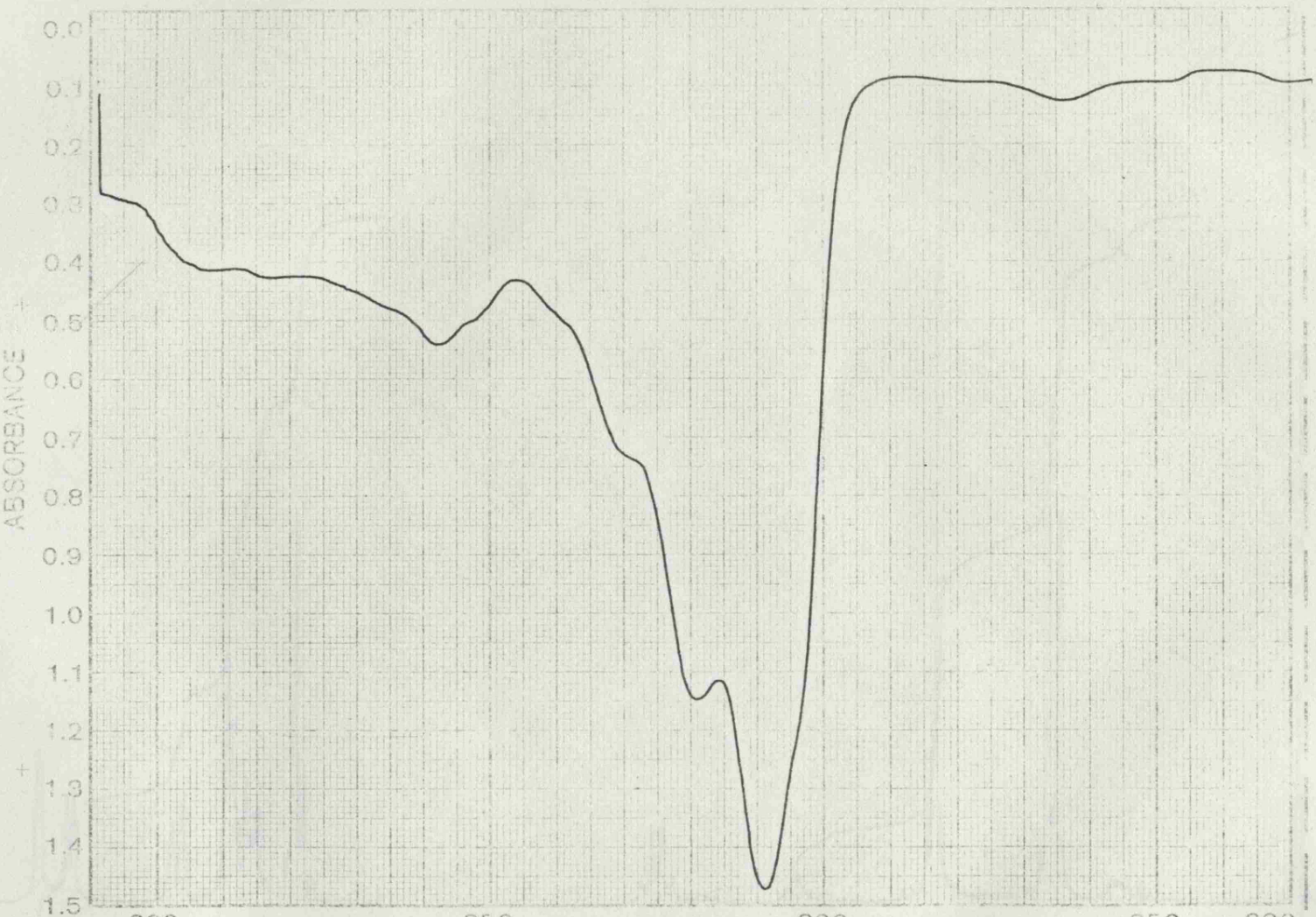
20

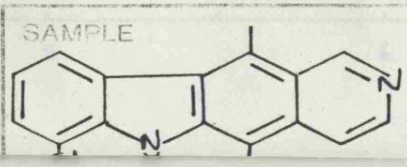
4.6.81

Harry

0 ppm


2·5
3
MICRONS
4
5
6
7
8
9
10
12
14
16
20
25
100
80
60
40
20
0
4000
3000
2000
1800
1600
1400
1200
1000
800
600
400
WAVENUMBER (CM⁻¹)
SAMPLE
SOLVENT KBr
CONC.
CELL PATH
REFERENCE
SCAN
SLIT
OPERATOR
DATE
SINGLE B.
T.D. SPEED
ORD. EXP.
T. CONST
REMARKS
PERKIN ELMER
PART No. 5102 1000
REF No.

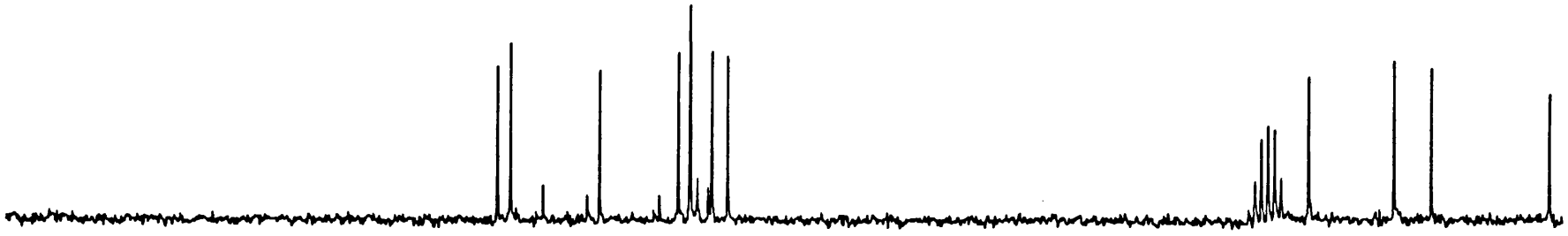


SAMPLE 	SOLVENT EtOH	SCAN
	CONC.	SLIT
	CELL PATH	OPERATOR
	REFERENCE	DATE

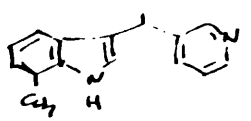
REMARKS

REF. No

ppm
0
2
4
6
8
10
DMSO
TMS



OK4.



3.210 S.

T. 2 S.
6T.

33.45
5'4.5

4 2
1.0

fil
0.4 F5' +

5000

22

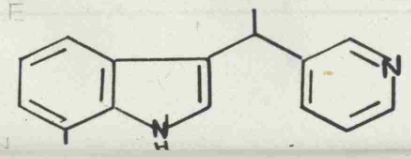
AUTO.

H 7

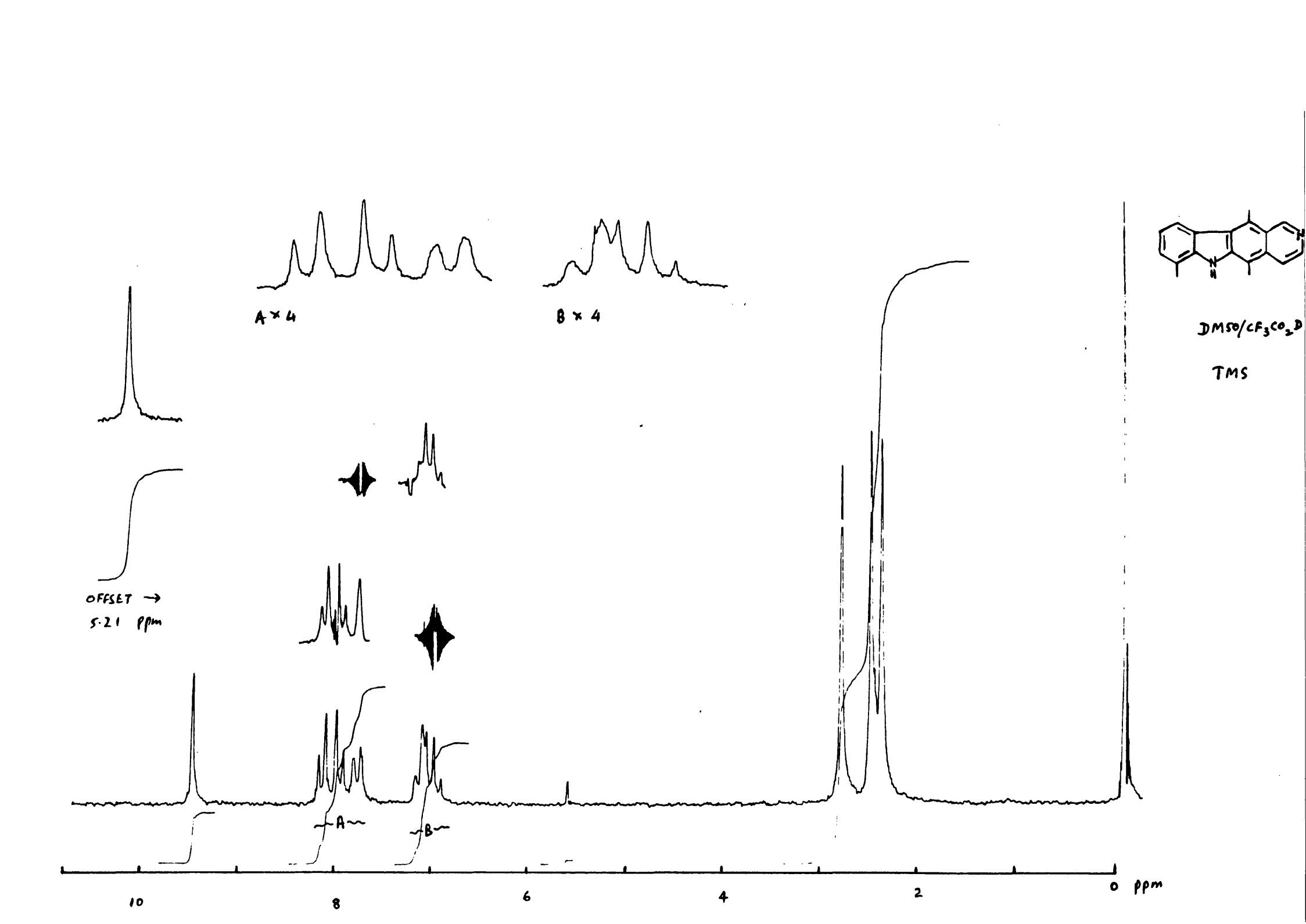
20

16.4. F1
11.

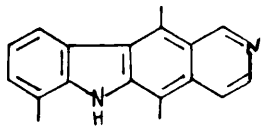
POIFI.

SAMPLE 	SOLVENT KBr.	SCAN	SINGLE B.
	CONC.	SLIT	T.D. SPEED
	CELL PATH	OPERATOR	ORD. EXP.
	REFERENCE	DATE	T. CONST
ORIGIN	PERKIN ELMER	PART No. 5102 1000	REF. No.

REMARKS


A × 4
B × 4
OFFSET →
5·21 ppm
A
B
10
8
6
4
2
0 ppm
DMSO/CF3CO2D
TMS

DKE 4



+TFA
DMSO 5

TMS
RT

✓

33·45
54·5
✓
4 3c
1.0

8/c
0.4857
5,00c

5,00c

22

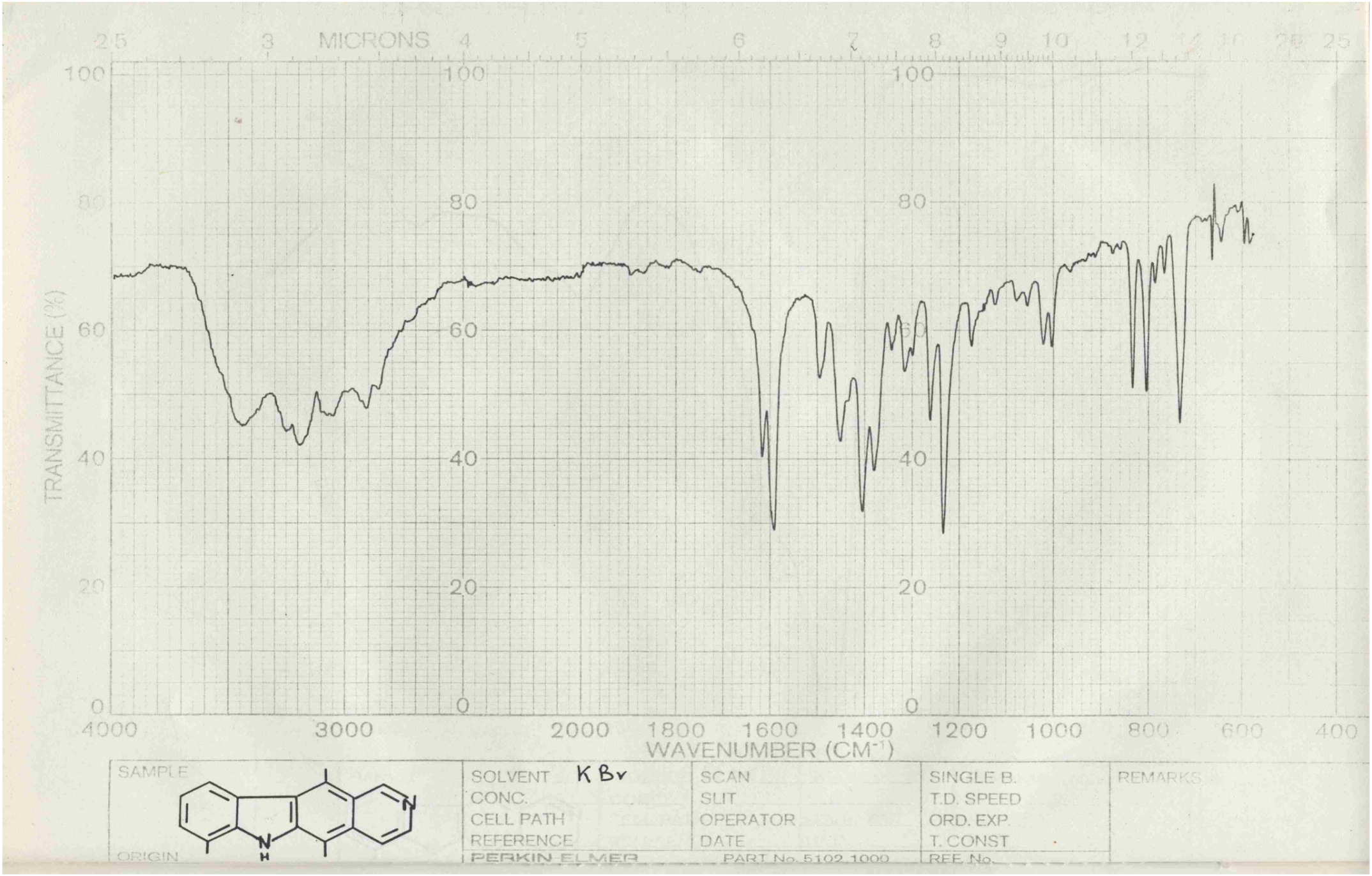
Auto

HS

20

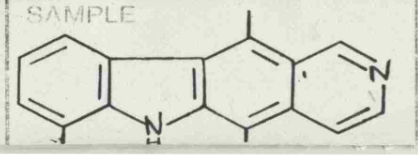
5-6-8:
Harry

0 ppm



SAMPLE	SOLVENT KBr	SCAN	SINGLE B.
	CONC.	SLIT	T.D. SPEED
	CELL PATH	OPERATOR	ORD. EXP.
	REFERENCE	DATE	T. CONST
ORIGIN	PERKIN-ELMER	PART No. 5102-1000	REF. No.

REMARKS

SAMPLE 	SOLVENT EtOH	SCAN	REMARKS
	CONC.	SLIT	
	CELL PATH	OPERATOR	
	REFERENCE	DATE	
			REF. No.

ppm
0
2
4
6
8
10
A
A×4
CDCl3
TMS

ppm
0
2
4
6
8
10
deuterated
DMSO
TMS